Surgical Oncology Manual

Second Edition

Frances C. Wright
Jaime Escallon
Moises Cukier
Melanie E. Tsang
Usmaan Hameed
Editors

Springer

Surgical Oncology Manual

Frances C. Wright • Jaime Escallon
Moises Cukier • Melanie E. Tsang
Usmaan Hameed
Editors

Surgical Oncology Manual

Second Edition

Springer

Editors
Frances C. Wright, MD, MEd, FRCSC
Department of Surgery
University of Toronto
Toronto, ON, Canada

Jaime Escallon, MD, FRCSC, FACS
Department of Surgery
University of Toronto
Toronto, ON, Canada

Moises Cukier, MD
Department of Surgical Oncology
National Cancer Institute
Panama City, Panama

Melanie E. Tsang, MD, MSc, FRCSC
General Surgical Oncology
University of Toronto
Toronto, ON, Canada

Usmaan Hameed, MD, FRCSC
General Surgical Oncology
University of Toronto
Toronto, ON, Canada

Originally published by the Department of Surgery, University of Toronto, Canada (March 25, 2013)

ISBN 978-3-319-26274-1 ISBN 978-3-319-26276-5 (eBook)
DOI 10.1007/978-3-319-26276-5

Library of Congress Control Number: 2015954633

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Foreword

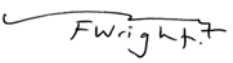
Dear Colleagues,

I am delighted to present the second edition of the *Surgical Oncology Manual*, previously published as *The University of Toronto Surgical Oncology Manual*. This is a collaborative work between the breast, hepatopancreatobiliary and general surgical oncology fellowship programs at the University of Toronto and our colleagues in medical oncology, radiation oncology and pathology. The manual represents a concise, usable and practical guide for the busy resident, fellow and staff person looking for the latest information on cancers treated by general surgeons.

The focus of this manual is up-to-date surgical treatment of cancers treated by general surgeons; however due to the intrinsic multi-disciplinary nature of oncology treatment, we have also included a discussion of systemic and radiation treatment and how these treatments interact with surgery. The easy-to-read format with tables enables the reader to gather information at a glance. In addition to presenting the latest evidence in surgical oncology, we also discuss practical "how we do it" tips and tricks.

I am truly grateful for the many hours of work the authors and editors have put into this second edition as well as the feedback we received about the first edition that we have incorporated into this book.

Yours sincerely,



Frances C. Wright
Toronto, ON, Canada

Acknowledgements

To all fellows and staff for their invaluable contributions.

To the General Surgery Oncology Fellowship Program for their financial support.

Contents

Contributors

Shady Ashamalla, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Nancy Baxter, MD, PhD, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Martin Blackstein, MD, PhD, FRCPC, FACP Department of Medicine, University of Toronto, Toronto, ON, Canada

Jean-François Boileau, MD, MSc, FRCSC Department of Surgery, Montreal Jewish General Hospital, Seagal Cancer Centre, Montreal, QC, Canada

Savtaj S. Brar, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Marcus J. Burnstein, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Charles Catton, MD, FRCPC Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada

Dan Charleton, MD, FRCSC Breast Surgery, University of Toronto, Toronto, ON, Canada

Tulin Cil, MD, MEd, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Sean Cleary, MD, MSc, MPH, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Natalie G. Coburn, MD, MPH, FRCSC, FACS Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada

Zane Cohen, MD, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Juan Camilo Correa, MD General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Mark Corrigan, MB, BAO, BCh, BMedSCI, MD, FRCSI Department of Surgery, Cork University Hospital, Cork, Ireland

Moises Cukier, MD Department of Surgical Oncology, National Cancer Institute, Panama City, Panama

Bernard Cummings, MB, ChB, FRCPC, FRCR, FRANZCR, Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada

Karen Devon, MD, MSc, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Brendan Dickson, MD, MSc, FCAP, FRCPC Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

Alexandra M. Easson, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Gareth Eeson, MD, MSc, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Jaime Escallon, MD, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Peter C. Ferguson, MD, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Steven Gallinger, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Ralph George, MD, PhD, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Mai-Kim Gervais, MD, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Rebecca A. Gladdy, MD, PhD, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Anand Govindarajan, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Paul D. Greig, MD, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Robert Gryfe, MD, PhD, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Abha Gupta, MD, MSc, FRCPC Division of Medical Oncology, University of Toronto, Toronto, ON, Canada

Julie Hallet, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Usmaan Hameed, MD, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Trevor D. Hamilton, MD, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Lucy Kathryn Helyer, MD, MSc, CCFP, FRCSC Department of Surgery, Queen Elizabeth II Health Sciences Centre, Halifax, NS, Canada

Claire Holloway, MD, PhD, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Nicole J. Look Hong, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Shiva Jayaraman, MD, MESc, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Anthony M. Joshua, MBBS, PhD, FRACP Department of Medical Oncology, University of Toronto, Toronto, ON, Canada

Paul J. Karanicolas, MD, PhD, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Peter T.W. Kim, MD, FRCSC, FACS Baylor University Medical Center, Annette C. and Harold C. Simmons Transplant Institute, Texas A&M Health Science Center, College of Medicine, Dallas, TX, USA

Girish S. Kulkarni, MD, PhD, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Calvin H.L. Law, MD, MPH, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Joan E. Lipa, MD, MSc, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Andrea MacNeill, MD, MSc, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Jessica Maxwell, MD, FRCSC Breast Surgery, University of Toronto, Toronto, ON, Canada

J. Andrea McCart, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

David R. McCready, MS, MSc, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Robin McLeod, MD, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Carol-anne E. Moulton, MD, PhD, FRACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Vanessa Palter, MD, PhD, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Teresa Petrella, MD, MSc, FRCPC Department of Medical Oncology, University of Toronto, Toronto, ON, Canada

Fayez A. Quereshy, MD, MBA, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Jennifer Racz, MD, MBA, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

Paul F. Ridgway, MD, MMedSc, FRCSI Department of Surgery, Trinity College Dublin at Tallaght Hospital, Dublin, Ireland

Amanda Roberts, MD, MPH, FRCSC Breast Surgery, University of Toronto, Toronto, ON, Canada

Lorne E. Rotstein, MD, FACS, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Corwyn Rowsell, MD, FRCPC, FCAP Department of Laboratory, Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada

Gonzalo Sapisochin, MD Hepatopancreatobiliary Surgery, University of Toronto, Toronto, ON, Canada

Simron Singh, MD, MPH, FRCPC Department of Medicine, University of Toronto, Toronto, ON, Canada

Amélie Tremblay St-Germain, MD, FRCSC Hepatopancreatobiliary Surgery, University of Toronto, Toronto, ON, Canada

Peter K. Stotland, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Alexander Sun, MD, FRCPC Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada

Robert Tasevski, MBBS, MSc, FRACS Department of Surgery, University of Melbourne, Melbourne, Australia

Koji Tomiyama, MD, PhD Hepatopancreatobiliary Surgery, University of Toronto, Toronto, ON, Canada

Melanie E. Tsang, MD, MSc, FRCSC General Surgical Oncology, University of Toronto, Toronto, ON, Canada

David R. Urbach, MD, MSc, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Alice C. Wei, MD, MSc, FRCSC, FACS Department of Surgery, University of Toronto, Toronto, ON, Canada

Frances C. Wright, MD, MEd, FRCSC Department of Surgery, University of Toronto, Toronto, ON, Canada

Chapter 1
Tumours of the Adrenal Gland

Vanessa Palter, Karen Devon, Julie Hallet, Girish S. Kulkarni, Calvin H.L. Law, and David R. Urbach

Introduction

Tumours of the adrenal gland are relatively common. They can be classified as functional or non-functional, benign or malignant or arising from the adrenal cortex versus the medulla.

Primary Adrenocortical Tumours

The majority of adrenocortical tumours are benign, non-functioning adenomas that are incidentally discovered on abdominal imaging for an unrelated cause (adrenal incidentaloma). Depending on the size of the lesion and the imaging modality utilized, the incidentaloma detection rate ranges from 1 to 10 % [1].

A lesser number present as benign functional tumours. 5–47 % of these present with symptoms of excess cortisol, and 1–3 % present with hyperaldosteronism. Rarely do patients present with virilizing hormone excess [2].

Adrenocortical carcinomas (ACCs) are rare tumours occurring with an incidence of 2 per million patients per year. ACC has a bimodal age distribution with increased incidence in children <6 years and in adults in their 40s and 50s [3]. ACCs may be either non-functional or associated with symptoms of hormonal excess.

V. Palter, M.D., Ph.D., F.R.C.S.C. (✉)
General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: vanessa.palter@mail.utoronto.ca

K. Devon, M.D., M.Sc., F.R.C.S.C., F.A.C.S. • J. Hallet, M.D., M.Sc., F.R.C.S.C.
G.S. Kulkarni, M.D., Ph.D., F.R.C.S.C. • C.H.L. Law, M.D., M.P.H., F.R.C.S.C.
D.R. Urbach, M.D., M.Sc., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: karen.devon@wchospital.ca; julie.hallet@sunnybrook.ca; girish.kulkarni@uhn.ca; calvin.law@sunnybrook.ca; david.urbach@uhn.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_1

The remainder of primary adrenocortical tumours are benign lesions that do not require resection such as myolipomas or congenital cysts.

Pheochromocytomas

Pheochromocytomas are catecholamine-producing tumours that arise from the enterochromaffin cells of the adrenal medulla. They may be benign or malignant. The rate of malignancy in pheochromocytomas has been reported to range from 3 to 36 % [3, 4].

Pheochromocytomas are responsible for less than 0.2 % of patients with hypertension, but if identified can be managed surgically and are potentially completely curable [4]. They are classically known as the "10 % tumour" with 10 % bilateral, 10 % malignant, 10 % extra-adrenal and 10 % familial.

Metastatic Tumours

In patients with no history of malignancy, less than 1 % of adrenal tumours represent metastatic disease. In patients with a history of malignancy, however, 70 % of adrenal tumours represent metastases from other sites.

Adrenocortical Tumours

Benign Functioning Adrenocortical Tumours

Adrenal Vein Sampling

- The identification of a mass on CT in a patient with primary aldosteronism does not necessarily establish a cause-and-effect relationship, due to the frequency of non-functioning incidental adrenal adenomas.
- Can be omitted in patients where aldosterone-producing adenoma is very likely (must fulfill all criteria) [7]
  - Patients ≤40y
  - Plasma aldosterone concentration ≥30 ng/dL
  - CT scan showing a hypodense (Hounsfield units ≤10) mass ≥1 cm
- All other patients should undergo adrenal vein sampling prior to definitive surgical management
- Procedure [8]
  - Confirm adrenal cannulation: adrenal vein-to-IVC cortisol ratio >5:1 with cosyntropin infusion
  - Assess unilateral hypersecretion: cortisol-corrected aldosterone ratio affected side:non-affected side ≥4:1

Work-up and management of benign functioning adrenocortical tumours

Clinical scenario	Work-up			Management		
	History and physical	Labs	Imaging	Peri-operative	Surgical	Non-surgical
Aldosterone producing (Zona glomerulosa)	• Hypertension • Hypokalemia (inconsistent) • Headaches, fatigue, polydipsia, polyuria, nocturia	• K+/Na+/Mg++ • Initial testing: Plasma aldosterone/renin ratio • Confirmatory testing (one of the following) [5] positive if lack of aldosterone or aldosterone/renin ratio suppression – Oral Na load with 24-h urine aldosterone (diet with >200 mEq/day of Na× 3 days) – IV Na load and plasma aldosterone measurement (2–3 L of NaCl 0.9 % over 4–6 h) – Fludrocortisone suppression and aldosterone/renin ratio measurement – Captopril challenge	• Thin-cut adrenal CT ±MRI • Adrenal vein sampling (see below)	Pre-operative • Control of HTN • Manage hypokalemia – Spironolactone – Potassium supplementation Post-operative • Measure serum aldosterone on post-op day 1 • d/c spironolactone and potassium supplementation • Decrease HTN meds if possible	• Adrenalectomy for confirmed aldosteronoma with lateralization on adrenal vein sampling. • 95 % resolution of hypokalemia, 90 % resolution of hypertension or significant reduction in need for anti-hypertensive medication.	• No lateralization with imaging modalities[a] • Bilateral involvement (cortical adrenal hyperplasia) • Treatment includes: K+-sparing diuretics and restriction of sodium intake (<100 mEq/day)

(continued)

(continued)

Clinical scenario	Work-up			Management		
	History and physical	Labs	Imaging	Peri-operative	Surgical	Non-surgical
Cortisol producing (Zona fasciculata)	• Weight gain • Proximal muscle weakness • Depression/psyc. symptoms • Easy bruising • Infections • Hypertension • Progressive central obesity, "moon face", dorso-cervical fat pad • Skin atrophy • Striae	Perform two of the following [6] (initial and 1 confirmatory tests): • Initial testing: 24-h urine-free cortisol (*x*2) • Confirmatory testing: – Low-dose (1 mg × 1) dexamethasone suppression test – High-dose (2 mg w6H × 48 h) dexamethasone suppression test Establish relationship with ACTH: serum ACTH—if <5 pg/mL, it is ACTH independent[c]	If ACTH is undetectable • Thin cut adrenal CT ± MRI • If not successful, perform adrenal vein sampling (see below)	Pre-operative • VTE prophylaxis (>10-fold greater risk of VTE) • Manage hyperglycaemia • Manage HTN Post-operative • Maintain glucocorticoid therapy—may need stress dosing • Manage hyperglycaemia	• Adrenalectomy[b] – Unilateral for confirmed cortisol producing tumor. – Bilateral for AIMAH or PPNAD	• If surgical treatment not possible or to control cortisol secretion while waiting for surgery • Agents include: metyrapone, ketoconazole
Androgen secreting (Zona reticularis)	• Hirsutism • Alopecia • Irregular menses • Acne	• DHEAS • Androstenedione • Testosterone • 17-OH progesterone • Serum estradiol	• Thin-cut adrenal CT ± MRI	• n/a	• Adrenalectomy for confirmed androgen producing tumor. • Low threshold for open resection if needed, due to higher malignancy risk.	• Limited number of cases reports.

ACTH adrenocorticotropic hormone, *DHEAS* 5-dehydroepiandrosterone steroid hormone, *MIBG* metaiodobenzylguanidine

[a]Subtypes of primary hyperaldosteronism: idiopathic hyperaldosteronism (65 %); aldosterone-producing adenoma (35 %); primary unilateral adrenal hyperplasia (3 %); aldosterone-producing ACC (1 %). Only aldosterone-producing adenoma and primary unilateral adrenal hyperplasia can be cured with surgery [7].

[b]Bilateral cortisol-secreting tumours are rare but can occur in MEN-1 and McCune-Albright syndrome; AIMAH: ACTH-independent macronodular adrenal hyperplasia (diffuse enlargement of bilateral adrenal glands); PPNAD: Primary pigmented nodular hyperplasia

[c]When ACTH is detectable consider non-adrenal pathology (MRI pituitary)

Adrenocortical Carcinoma

- ACC appears to be mostly sporadic; however it is associated with several hereditary cancer syndromes including [9]:
  - Li-Fraumeni syndrome or SBLA syndrome (sarcoma, breast cancer, lung cancer and ACC) [10]
  - Multiple endocrine neoplasia (MEN) type 1 (parathyroid, pituitary and pancreatic neuroendocrine tumours and adrenal tumours (ACC<<adrenal adenomas)) [11]
- 60 % of ACCs present with symptoms of hormone excess [3]
  - 40 % Cushing's syndrome alone
  - 25 % mixed virilization and Cushing's
  - <10 % virilization alone
  - <10 % feminizing (all feminizing tumours in men are malignant)
  - <10 % hyper-aldosteronism
- The recommended staging system is European Network for The Study of Adrenal Tumors (ENSAT) [12].

Prognostic Factors

1. Stage

Presentation	Prognosis 5-Year overall survival (OS)
• Tumour < 5 cm confined to the adrenal gland without local invasion	82 %
• Tumour > 5 cm confined to the adrenal gland without local invasion	61 %
• Any size, with any of the followings: infiltration to surrounding tissues, invasion to vena cava/renal vein or positive nodes	50 %
• Distant metastasis	13 %

2. Margin status
   - 5-Year overall survival rates for patients with ACC and uninvolved, microscopically involved and macroscopically involved margins are reported to be 46 %, 21 %, and 10 %, respectively [13].
3. Histology
   - Weiss' histological scoring system is based upon nine features (nuclear grade, mitotic rate, atypical mitoses, clear cell component, diffuse architecture, tumour necrosis, invasion of venous or sinus structures or tumour capsule) [14].

     Tumours with less than three features are usually considered benign [14].
   - Markers of proliferation (KI-67 and mitotic rate) also indicate poorer prognosis [15, 16].

4. Older age at diagnosis [17]
5. Hypersecretion of cortisol [17]

Work-up and management of ACC

Work-Up	Management		Follow-up (F/U)
	Localized disease	Metastatic disease	
• **History and physical exam** • **Labs** [18]: Glucocorticoid excess (3 of 4) – 1 mg dexamethasone suppression test – 24-h urine cortisol – Serum cortisol Sexual steroids and precursors – DHEAS – 17-OH progesterone – Androstenedione – Testosterone – 17 beta estradiol (men and pre-menopausal women) Mineralocorticoid excess – Plasma aldosterone:renin – Serum potassium Pheochromocytoma – 24-h urine for c/m – Plasma metanephrines • **Imaging**: – CT abdomen +/- MRI – CT chest – Bone scan—if clinically suspicious – PET—unilateral lesions difficult to distinguish from benign • Biopsy: ONLY if non-resectable and needed to initiate systemic therapy. Risk of seeding and limited usefulness in differentiating benign vs. malignant	• Surgical excision with en bloc resection of adjacent involved organs if needed • Consider adjuvant mitotane in selected cases based on[a] [19] • Tumour stage • Completeness of resection • Proliferation index • Consider adjuvant radiation therapy [20] – Incomplete resection – High tumour grade – Tumour spillage – Large size	• Complete resection of limited oligometastatic resectable disease in good surgical candidate has been shown to prolong survival in highly selected patients • Radiation for bony metastases if symptomatic • RFA or embolization for hepatic metastases • Mitotane monotherapy • Mitotane plus chemotherapy (etoposide, doxorubicin, cisplatin)	• Clinically: • Cushing's syndrome • Virilization syndrome • Labs and imaging (q 6 months): • Urinary cortisol • CT scan chest/abdo/pelvis for 5 years

c/*m* catecholamines and metanephrines, *ACTH* adrenocorticotropic hormone, *RFA* radiofrequency ablation

[a]Benefit in recurrence-free survival in a retrospective series of <200 patients

Pheochromocytoma

Genetics

- 25 % of patients with pheochromocytoma have an associated genetic syndrome [21]
  - These patients tend to present at a younger age and with bilateral disease
- Autosomal dominant familial disorders associated with adrenal pheochromocytoma
  - Von-Hippel-Lindau (VHL) [22]

    Pheochromocytoma (20 %); paraganglioma; hemangioblastoma; retinal angioma; renal cell carcinoma; pancreatic neuroendocrine tumours; cystadenomas of pancreas, broad ligament and epididymis
  - Multiple endocrine neoplasia type 2 (MEN-2) [22]

    Pheochromocytoma (50 %); medullary thyroid cancer (100 %); primary hyperparathyroidism (20 %); primary lichen amyloidosis (5 %)
    Only 3–5 % of pheochromocytoma in MEN-2 are malignant
  - Neurofibromatosis type 1 [22]

    Pheochromocytoma (2 %); café au lait patches; CNS gliomas; cognitive deficits; bony abnormalities
  - Familial pheochromocytoma [22]

    Germ-line mutations of genes encoding succinate dehydrogenase subunits B, C and D
    Individuals with succinate dehydrogenase B mutations are more likely to develop malignant disease [23]
- Genetic screening (any of the below)
  - Paraganglioma
  - Bilateral pheochromocytoma
  - Family history of pheochromocytoma or paraganglioma
  - Unilateral adrenal pheochromocytoma ≤45y
  - Clinical findings of genetic disorder

Benign Versus Malignant Disease

- Histology and biochemistry cannot definitively distinguish benign and malignant pheochromocytoma. If malignant disease is suspected by imaging (usually based on size >10 cm), then the patient should be staged with CT chest/abdo/pelvis, bone scan and MIBG study. The diagnosis of malignancy can only be made by the presence of local invasion or distant spread [4].
- Survival rates depend on the location of the metastatic lesions with short-term survivors (<5 years) possessing metastases to the lungs and liver, and longer term survivors (>5 year) manifesting metastatic lesions to bone. Overall 5-year survival rates vary between 30 and 60 % [4].

Management of pheochromocytoma

Work-up	Peri-operative management	Surgical management	Adjunctive therapy (malignant disease)	Follow-up
History and Physical • Episodic headache • Sweating • Tachycardia • Palpitations • Tremor • Hypertension **Laboratory Investigations** • 24-h urine for catecholamines and metanephrines • Plasma-free metanephrines • Consider confirmatory test – Clonidine suppression test **Imaging** • Thin-cut spiral CT • MRI abdomen • MIBG scan – Used when MRI/CT negative and diagnosis still suspected – >10 cm adrenal mass – paraganglionoma	**Pre-operative** • Alpha adrenergic blockade with phenoxybenzamine (non-competitive alpha blocker)—complete blockage is achieved when orthostatic hypotension and nasal congestion appear • Fluid and electrolyte balance • Beta-blockade after alpha-blockade, if needed, to protect against reflex tachycardia	**Benign Disease** Laparoscopic adrenalectomy • No malignant radiological features • ≤8–10 cm • Minimal tumour handling to decrease excess catecholamine surge • Division of adrenal vein early in process • Constant intra-operative communication with anesthesia **Malignant Disease** • Resect primary and metastatic lesions if possible • This reduces symptoms of hormone excess and can improve efficacy of subsequent treatment	**Chemotherapy** [24] • Consider in unresectable or rapidly growing tumours • Combination of vincristine, cyclophosphamide, dacarbazine, doxorubicin • ~50 % will respond **Radiation** • For bulky symptomatic primaries • Bony metastases **I-131 MIBG** [25] • If tumour takes up MIBG (60 % of tumours) • Response rate of 30 %	**Completely resected disease** • Q3–12 months – H&P – BP check – Plasma and urine metanephrines • Annually – Consider imaging **Incompletely resected disease** • Q3–4 months – H&P – BP check – Plasma and urine metanephrines – Imaging

Incidentally Discovered Adrenal Mass (Adrenal Incidentaloma)

- The overlying principle of management of adrenal incidentalomas is that all functioning lesions and non-functioning lesions at risk of representing malignant disease should be surgically removed. Small non-functioning lesions should be followed for interval growth, and managed accordingly [1].
- Lesions <4 cm have a risk of ACC of <2 % [26].
- Lesions >6 cm have a risk of ACC of >20 %.

Work-up and management of adrenal incidentaloma

Work-up	Management	Follow-up (F/U)
• History and physical exam • Labs: – 1 mg dexamethasone suppression test – 24-h urine cortisol – Plasma-free metanephrines – 24-h urine c/m – PRA if HTN – Serum DHEA-S (only if symptoms suggestive of virilizing tumour) • Fine-needle biopsy ONLY if history of malignancy and ONLY after pheochromocytoma ruled out	• Surgical resection if functioning • If non-functioning, then resection based on size: – <4 cm—observation – 4–6 cm—individualize treatment[a] – >6 cm—resection	• If resection due to functioning tumour: – Physiologic tests q 6 months for 2 years – CT scans only if abnormal biochemical tests or malignant disease • If no resection and tumour < 4 cm: – Abdominal US q 6 months for 2 years – If no interval increase stop imaging

HTN hypertension, *US* ultrasound, *c/m* catecholamines and metanephrines, *PRA* plasma aldosterone/renin

[a]Resection recommended in younger patients or in patients with any imaging features concerning for ACC (see Imaging Characteristics of Adrenal Masses)

Special Notes: Imaging Characteristics of Adrenal Masses

- Benign adenoma
  - Small homogeneous well-defined lesions
  - <10HU on non-enhanced CT scan
  - Enhanced CT scan with 15-min washout ≥40 %
  - Low T2 signal intensity on MRI
  - Loss of signal intensity on opposed-phase chemical shift sequences on MRI
- Adrenocortical Carcinoma
  - Large, heterogeneous, irregular lesions or those that invade surrounding structures
  - >18HU on non-enhanced CT scan
  - Enhanced CT scan with 15-min washout ≤ 40 %
  - Bright on T2-weighted MRI images
  - No loss of signal intensity on opposed-phase MRI images

- Pheochromocytoma
  - Increased vascularity
  - >20HU on non-enhanced CT scan
  - <50 % washout at 15 min on contrast-enhanced CT scan
  - High T2 signal on MRI
- Adrenal Metastases
  - Irregular non-homogeneous
  - >20HU on non-enhanced CT scan
  - <50 % washout after 15 min on contrast-enhanced CT scan
  - Intermediate to high intensity on T2-weighted MRI
  - Elevated uptake on FDG-PET

Metastases to the Adrenal Gland

- Most common cause of adrenal incidentaloma in patients with history of malignant disease
- The adrenal gland is the fourth most common site of metastasis after the lungs, liver and bone
- Most common primaries
  - Lung, breast, melanoma, kidney, thyroid and colon cancer
- Fine-Needle Aspiration Biopsy
  - Cannot differentiate between adrenal adenoma and adrenocortical carcinoma
  - Can differentiate between adrenal tumour and metastatic disease
  - Therefore clinically indicated if known malignancy or suspected malignancy outside of adrenal [12]
  - MUST rule out pheochromocytoma prior to biopsy and is ONLY indicated if high suspicion of metastatic disease that cannot be documented by biopsy of other tissue
- Potential benefit in survival for selected patients
  - Non-small-cell lung cancer: 5y-OS 25 %
  - Colorectal cancer: mean survival 13–30 months

Toronto Pearls

Surgical Approach

- Preferred approach for resection of adrenal tumours <7 cm is minimally invasive surgery either laparoscopic transabdominal or retroperitoneal approach

  - For laparoscopic transabdominal approach, the patient is in lateral decubitus position.
  - For retroperitoneal approach, the patient is in prone jack-knife position. This approach, however, has a much steeper learning curve than the laparoscopic transabdominal approach. It is especially well suited for patients with hostile abdomen due to multiple prior abdominal surgeries.

- Open approach should be recommended for patients with
  - Large tumours (>10 cm) (even with benign features on imaging)
  - Evidence of local invasion
  - Features consistent with ACC on either CT or MRI

References

1. Grumbach MM, Biller BM, Braunstein GD, et al. Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med. 2003;138(5):424–9.
2. Mansmann G, Lau J, Balk E, et al. The clinically inapparent adrenal mass: update in diagnosis and management. Endocr Rev. 2004;25(2):309–40.
3. Ng L, Libertino JM. Adrenocortical carcinoma: diagnosis, evaluation and treatment. J Urol. 2003;169(1):5–11.
4. Harari A, Inabnet 3rd WB. Malignant pheochromocytoma: a review. Am J Surg. 2011; 201(5):700–8.
5. Funder JW, Carey RM, Fardella C, et al. Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2008;93(9):3266–81.
6. Nieman LK, Biller BM, Findling JW, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008;93(5):1526–40.
7. Mattsson C, Young Jr WF. Primary aldosteronism: diagnostic and treatment strategies. Nat Clin Pract Nephrol. 2006;2(4):198–208. quiz, 1 p following 230.
8. Young WF, Stanson AW, Thompson GB, et al. Role for adrenal venous sampling in primary aldosteronism. Surgery. 2004;136(6):1227–35.
9. Koch CA, Pacak K, Chrousos GP. The molecular pathogenesis of hereditary and sporadic adrenocortical and adrenomedullary tumors. J Clin Endocrinol Metab. 2002;87(12):5367–84.
10. Hisada M, Garber JE, Fung CY, et al. Multiple primary cancers in families with Li-Fraumeni syndrome. J Natl Cancer Inst. 1998;90(8):606–11.
11. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658–71.
12. Fassnacht M, Johanssen S, Quinkler M, et al. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. Cancer. 2009;115(2):243–50.
13. Bilimoria KY, Shen WT, Elaraj D, et al. Adrenocortical carcinoma in the United States: treatment utilization and prognostic factors. Cancer. 2008;113(11):3130–6.
14. Weiss LM, Medeiros LJ, Vickery Jr AL. Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol. 1989;13(3):202–6.
15. Stojadinovic A, Ghossein RA, Hoos A, et al. Adrenocortical carcinoma: clinical, morphologic, and molecular characterization. J Clin Oncol. 2002;20(4):941–50.
16. Morimoto R, Satoh F, Murakami O, et al. Immunohistochemistry of a proliferation marker Ki67/MIB1 in adrenocortical carcinomas: Ki67/MIB1 labeling index is a predictor for recurrence of adrenocortical carcinomas. Endocr J. 2008;55(1):49–55.

17. Abiven G, Coste J, Groussin L, et al. Clinical and biological features in the prognosis of adrenocortical cancer: poor outcome of cortisol-secreting tumors in a series of 202 consecutive patients. J Clin Endocrinol Metab. 2006;91(7):2650–5.
18. http://www.ensat.org/page-1317312. Accessed Oct 4 2014.
19. Terzolo M, Angeli A, Fassnacht M, et al. Adjuvant mitotane treatment for adrenocortical carcinoma. N Engl J Med. 2007;356(23):2372–80.
20. Polat B, Fassnacht M, Pfreundner L, et al. Radiotherapy in adrenocortical carcinoma. Cancer. 2009;115(13):2816–23.
21. Neumann HP, Bausch B, McWhinney SR, et al. Germ-line mutations in nonsyndromic pheochromocytoma. N Engl J Med. 2002;346(19):1459–66.
22. Chen H, Sippel RS, O'Dorisio MS, et al. The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer. Pancreas. 2010;39(6):775–83.
23. Gimenez-Roqueplo AP, Favier J, Rustin P, et al. Mutations in the SDHB gene are associated with extra-adrenal and/or malignant phaeochromocytomas. Cancer Res. 2003;63(17):5615–21.
24. Averbuch SD, Steakley CS, Young RC, et al. Malignant pheochromocytoma: effective treatment with a combination of cyclophosphamide, vincristine, and dacarbazine. Ann Intern Med. 1988;109(4):267–73.
25. Rose B, Matthay KK, Price D, et al. High-dose 131I-metaiodobenzylguanidine therapy for 12 patients with malignant pheochromocytoma. Cancer. 2003;98(2):239–48.
26. Angeli A, Osella G, Ali A, Terzolo M. Adrenal incidentaloma: an overview of clinical and epidemiological data from the National Italian Study Group. Horm Res. 1997;47(4-6):279–83.

Chapter 2
Ampullary Cancer

Gareth Eeson, Sean Cleary, Carol-anne E. Moulton, and Paul F. Ridgway

Introduction

Periampullary neoplasms arise in proximity of the ampulla of Vater (within 2 cm) and can originate from the duodenum, pancreatic head, distal common bile duct or the ampullary complex. Ampullary tumours proper are those arising directly from the structures of the ampullary complex distal to the confluence of the bile duct and pancreatic duct and represent roughly 7 % of periampullary neoplasms. These rare tumors represent 0.5 % of all GI cancers, though a subtle increase of 0.9 % per year has been observed in recent decades [1].

Ampullary carcinoma carries a notably more favourable prognosis than other pancreaticobiliary malignancies. This is likely attributed to an earlier stage of disease at clinical presentation and a potentially more favourable disease biology. Curative-intent resection is possible in 50 % of patients presenting with ampullary cancer compared with 10 % for patients with pancreatic cancer [2]. Specific risk factors for ampullary cancer have not been identified but duodenal adenomas and peri-ampullary malignancies are a well-described feature of the familial adenomatous polyposis syndrome.

G. Eeson, M.D., M.Sc., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology University of Toronto, Toronto, ON, Canada
e-mail: gareth.eeson@sunnybrook.ca

S. Cleary, M.D., M.Sc., M.P.H., F.R.C.S.C., F.A.C.S. • C.-a.E. Moulton, M.D., Ph.D., F.R.A.C.S.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: Sean.Cleary@uhn.ca; Carol-anne.Moulton@uhn.ca

P.F. Ridgway, M.D., M.Med.Sc., F.R.C.S.I.
Department of Surgery, Trinity College Dublin at Tallaght Hospital, Dublin, Ireland
e-mail: PRidgway@rcsi.ie

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_2

The large majority of ampullary cancers are adenocarcinoma and are broadly categorised as (1) pancreaticobiliary and (2) intestinal histologic subtypes based on their epithelial origin. Intestinal-type tumours have a more favourable prognosis compared with pancreaticobiliary type (~60 % vs. ~20 % at 5 years; median OS 116 vs. 22 months) [3, 4]. Lymph node positivity is among the strongest prognostic factors and is closely correlated with the size of the primary tumour: >1 cm = 9 %, 1–1.5 cm = 25 %, and >1.5 cm 40–50 % [4]. The recommended staging system is the International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC) 7th edition [5].

Presentation	Prognosis 5-year overall survival (OS) [1]
• Local	45 %
• Regional	31 %
• Distant	4 %

Several factors conspire against the formulation of large prospective randomised studies for ampullary carcinoma including the rarity of the disease, histologic heterogeneity and the amalgamation with other pancreaticobiliary cancers. As such, no prospective studies exclusively evaluating ampullary carcinoma have been published and management recommendations are based largely on extrapolation from the management of pancreatic adenocarcinoma and consensus guidelines.

Management

Resectable Ampullary Adenocarcinoma

Clinical scenario	Work-up	Surgical management	Adjuvant therapy	Follow-up (F/U)
Benign adenoma	• History and physical exam • Labs: – Ca 19-9, CEA • Staging: – CT chest, biphasic CT abdo/pelvis – MRI/MRCP – +/– EUS to evaluate the extent of local invasion or for biopsy – +/– Staging laparoscopy[a] • Consider biliary decompression if jaundice present (ERCP or PTC) and immediate resection not available	• **Local resection** recommended: endoscopic resection, duodenotomy with polypectomy and/or ampullectomy[a] [6]	• No adjuvant therapy indicated	• Following local resection surveillance is required with a side-viewing endoscope
In situ disease		• **Pancreaticoduodenectomy** should be considered for high-grade dysplasia/in situ disease in young patients and good performance status; otherwise local excision is recommended		• CT chest/abdo/pelvis every 3–6 months for the first 2 years, then every 6 months to 1 year thereafter
Invasive disease		• **Pancreaticoduodenectomy** recommended [6] – Local resection for cT1 disease is associated with R1 resection rate of 25–60 % and higher local recurrence. Not recommended for good operative candidates. • Lymphadenectomy: – Routine LN dissection includes peri-pancreatic, CBD and pyloric nodes – Extended LN dissection not indicated as no demonstrated improvement in outcomes	• No consensus of optimal therapy • Consider: – Chemotherapy alone[a] – Chemoradiotherapy[a] – Observation	

MRCP magnetic resonance cholangiopancreatography, *ERCP* endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *EUS* endoscopic ultrasound, *LN* lymph node

[a]See Special Notes

Special Notes

- In Ontario, all patients with known or suspected ampullary adenocarcinoma should be referred for management at a high-volume hepatopancreaticobiliary surgical oncology centre.
- **Role of Frozen Section**: Frozen section is used to confirm metastatic/unresectable disease. In cases where a lesion is not endoscopically resectable, but is amenable to local resection (transduodenal ampullectomy), frozen section is used to determine margin status and to determine the need to proceed to pancreaticoduodenectomy.
- **Laparoscopic Staging** has limited use in upstaging ampullary carcinoma since the advent of high-quality multidetector CT. Appropriate in selected patients at increased risk of metastatic disease in the absence of unresectability on pre-operative imaging (e.g. elevated CA 19-9, larger tumours [7]).
- **Medical Oncology**: No consensus exists regarding optimal systemic therapy for ampullary carcinoma. The largest RCT evaluating adjuvant chemotherapy for resected peri-ampullary cancers ($n=297$ ampullary) showed a statistically non-significant improvement in overall survival with gemcitabine or 5-FU over observation alone. The role of molecular targeted agents remains to be evaluated in ampullary cancer. Patients should be referred for discussion of adjuvant therapy.
- **Radiotherapy**: The role of adjuvant radiation is controversial. Several observational studies suggest improved survival with chemoradiation (CRT) for tumours with adverse features (node positive, poorly differentiated, T3/T4) [8–11]. The only prospective RCT evaluating CRT for resected pancreatic and peri-ampullary cancers failed to demonstrate a survival benefit for the subgroup of mixed peri-ampullary tumours ($n=104$) [12].

Special Case: Familial Adenomatous Polyposis

- 50–90 % of patients diagnosed with FAP have duodenal adenomas.
- Overall lifetime risk of duodenal cancer is ~5 %.
- Duodenal cancer in FAP has a later onset than colorectal cancer (median age 52).
- FAP patients require regular side-viewing duodenoscopy and biopsy of suspicious lesions, starting at 25 years.
- A practical and effective surveillance strategy for upper GI malignancies in FAP patients has been developed at the University of Toronto and is described below [13].

Stage	Size (mm)	Histology	Management
1	0	Normal	EGD q 5 years
2	1–2	Adenoma	EGD q 3 years
3	2.1–10	Adenoma	EGD q6 months
4	2.1–10 >10	HGD Adenoma	Endoscopic or surgical resection
5	Any	Adenocarcinoma	Radical surgery (e.g. pancreaticoduodenectomy)

EGD esophagoduodenoscopy (with side-viewing scope), *HGD* high-grade dysplasia

Unresectable/Metastatic Ampullary Adenocarcinoma

Criteria of unresectability	Management
• Metastatic disease: – Liver, lung, peritoneum and distant lymph nodes (celiac, SMA nodes, tail of pancreas) • Patient factors: – Prohibitive co-morbidities or functional status • Anatomical factors: – Criteria similar to those applied to pancreatic head cancers, e.g. arterial encasement, portal vein involvement which precludes reconstruction	• Radical resection not indicated • Consider non-operative palliation interventions (e.g. stent/PTC placement) • Consider surgery for palliation only • Improved PFS and median survival have been demonstrated with platinum + anti-metabolite regimens [14, 15] • Consider radiotherapy

SMA superior mesenteric artery, *PTC* percutaneous transhepatic cholangiography/catheter, *PFS* progression-free survival

Landmark Trials

Prospective RCTs regarding the management of ampullary carcinoma are few, due to the relative rarity of the disease and inclusion in pancreatic adenocarcinoma trials. As such, treatment protocols have largely been extrapolated from trials evaluating peri-ampullary malignancies that included subsets of ampullary carcinoma [12, 16]. Surgical management is largely dictated by consensus statements [6].

Referring to Medical Oncology

1. Consider for all patients.
2. High-risk features (R1 resection, poorly differentiated, lymphovascular or perineural invasion, T3/T4, node positive, pancreaticobiliary histology).
3. Unresectable disease.

Referring to Radiation Oncology

1. High-risk features (R1 resection, poorly differentiated, lymphovascular or perineural invasion, T3/T4, node positive, pancreaticobiliary histology).
2. Palliative patients for consideration of symptomatic control.

Referring to Multidisciplinary Cancer Conference (MCC)

1. High-risk features (R1 resection, poorly differentiated, T3/T4, node positive, pancreaticobiliary histology).
2. Locally advanced disease.
3. Unresectable disease.

Toronto Pearls

- Biliary obstruction associated with ampullary lesions can be intermittent (ball-valve effect).
- Lesions with high-grade dysplasia or carcinoma in situ on endoscopic biopsies have high rate of invasive cancer on final pathology. Formal resection (pancreaticoduodenectomy) or intraoperative frozen section at ampullectomy should be considered in these patients.
- Formal pancreaticoduodenal resection should be considered for malignant ampullary lesions.
- Pylorus-preserving pancreaticoduodenectomy is generally not advised for ampullary lesions.
- Luminal obstruction by ampullary lesions can be palliated by endoscopic resection and/or endoluminal stent placement.

References

1. Albores-Saavedra J, et al. Cancers of the ampulla of vater: demographics, morphology, and survival based on 5,625 cases from the SEER program. J Surg Oncol. 2009;100(7):598–605.
2. O'Connell JB, et al. Survival after resection of ampullary carcinoma: a national population-based study. Ann Surg Oncol. 2008;15(7):1820–7.
3. Chang DK, et al. Histomolecular phenotypes and outcome in adenocarcinoma of the ampulla of vater. J Clin Oncol. 2013;31(10):1348–56.
4. Heinrich S, Clavien PA. Ampullary cancer. Curr Opin Gastroenterol. 2010;26(3):280–5.
5. Edge S, Byrd DR, Compton C, Fritz A, Greene F, Trotti A. American joint committee on cancer staging manual. New York: Springer; 2009.
6. Kondo S, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. J Hepatobiliary Pancreat Surg. 2008;15(1):41–54.
7. Alexakis N, et al. High serum CA 19-9 but not tumor size should select patients for staging laparoscopy in radiological resectable pancreas head and peri-ampullary cancer. Eur J Surg Oncol. 2015;41(2):265–9.
8. Bhatia S, et al. Adjuvant therapy for ampullary carcinomas: the Mayo Clinic experience. Int J Radiat Oncol Biol Phys. 2006;66(2):514–9.
9. Narang AK, et al. Evaluation of adjuvant chemoradiation therapy for ampullary adenocarcinoma: the Johns Hopkins Hospital-Mayo Clinic collaborative study. Radiat Oncol. 2011;6:126.

10. Kim K, et al. Role of adjuvant chemoradiotherapy for ampulla of Vater cancer. Int J Radiat Oncol Biol Phys. 2009;75(2):436–41.
11. Krishnan S, et al. Role of adjuvant chemoradiation therapy in adenocarcinomas of the ampulla of vater. Int J Radiat Oncol Biol Phys. 2008;70(3):735–43.
12. Klinkenbijl JH, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776–82. discussion 782-4.
13. Serrano PE, et al. Progression and management of duodenal neoplasia in familial adenomatous polyposis: a cohort study. Ann Surg. 2015;261(6):1138–44.
14. Valle J, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.
15. Overman MJ, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol. 2009;27(16):2598–603.
16. Neoptolemos JP, et al. Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. JAMA. 2012;308(2):147–56.

Chapter 3
Anal Cancer

Juan Camilo Correa, Bernard Cummings, and Alexandra M. Easson

Introduction

Anal cancer is an uncommon gastrointestinal tract cancer, representing 1.5 % of all GI malignancies [1]. There are approximately 500 cases of anal cancer per year in Canada, with an annual incidence rate of about 1 per 100,000 men and 1.5 per 100,000 women [2]. The incidence of anal canal carcinoma (ACC) has risen in recent decades for causes which are unclear. There is an increased incidence in immunosuppressed individuals, up to about 6.3–12.3 per 100,000 in solid organ transplant patients [3, 4], and to about 70 per 100,000 in HIV-infected men who have sex with men (MSM) [5, 6].

Definitions/Terminology

- **Anal Canal:** The anal canal extends from the upper border of the anal sphincter and puborectalis muscles to the lowermost edge of the sphincter complex corresponding to the anal verge or introitus of the anal orifice. Historically, differences

J.C. Correa, M.D. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: jcccote@yahoo.com

B. Cummings, M.B., Ch.B., F.R.C.P.C., F.R.C.R., F.R.A.N.Z.C.R.
Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada
e-mail: bernard.cummings@rmp.uhn.on.ca

A.M. Easson, M.D., M.Sc., F.R.C.S.C
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: alexandra.easson@uhn.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_3

in histological characteristics of the mucosal lining of the anal canal were used in determining management. The treatment of anal canal tumours has been standardized for all squamous cell carcinomas irrespective of histological subtype (squamous, keratinizing or non-keratinizing, transitional, basaloid, urothelial, or cloacogenic epithelium) [7, 8].

- **Anal Margin/Perianal Skin:** The perianal skin (anal margin) begins at the anal verge and extends as pigmented epidermis over a 5 cm radius from the anal verge. It is further defined by the presence of epidermal appendages. Where cancer involves both perianal skin and the anal canal, and the site of origin is uncertain, it is usual to stage and treat such cancers as anal canal cancers.

Approximately 85–90 % of the anal canal cancers are squamous cell type and 10–15 % are adenocarcinomas, with small numbers of undifferentiated and small cell cancers. Historically, anal canal carcinomas were treated with radical surgery using an abdominoperineal resection. Following the introduction of a preoperative chemoradiation protocol by Nigro et al. in 1974 [9], treatment paradigms shifted towards a combined modality approach, with surgery largely reserved for treatment salvage.

Natural History and Precursor Lesions

Anal cancer has been related to a latent human papillomavirus infection (HPV), found in up to 90 % of anal canal squamous cell cancers, and about 60 % of perianal cancers [2, 10]. HPV infection in immunocompetent patients is cleared in more than 90 % of patients within 2 years [11, 12]; this clearance is lower in immunocompromised patients. There are many HPV serotypes that have been related to the development of ACC, HVP 16 and 18 being the most common, present in up to 78–90 % of cases [13, 14].

Cigarette smoking is a recognized risk factor for anal cancer [15]. Benign anal conditions such as hemorrhoids and fissures, and inflammatory bowel diseases, are not associated with an increased risk of anal cancer [16].

Anal cancer may arise directly, or from a precursor dysplastic lesion, known as anal intraepithelial neoplasia (AIN) (generally considered low grade or AIN I, or high grade (AIN II or III)). High-grade AIN is present in 20–30 % of all men who have sex with men (MSM), approximately 40 % of HIV-positive MSM, 3 % of HIV-negative men, 63 % of women with cervical cancer, 9 % of HIV-positive women, and 5 % of HIV-negative women [17, 18].

The progression of high-grade AIN (HGAIN) to anal canal carcinoma is low, around 5–10 % in long-term follow-up [17, 19, 20], but treatment may prevent the development of ACC [7].

The treatment options for AIN are characterized by a high degree of recurrence, being up to 50 % or more at 1 year of follow-up. Only 13 % of HIV-positive and 26 % of HIV-negative patients were free of disease recurrence at 6 years of follow-up [19, 21].

	Work-up	Treatment		Follow-up (F/U) (time after primary treatment)
		Primary	Recurrence	

AIN II/III or HGAIN	• Comprehensive history
	• Digital rectal examination
	• High-resolution anoscopy (HRA) with acetic acid 3 % and Lugol's iodine
	• Gynecological examination in women, with cervical cancer screening as appropriate
		• Watchful waiting with HRA every 4–6 months
		• Medical therapies:
		  • Topical 5 % imiquimod cream three times per week for 16 weeks. Response rates 48–86 % [14, 20]
		  • Cidofovir 1 % gel used for 6 weeks. Treatment successful in all low-risk HPV and 57 % of high-risk HPV. Recurrence 35 % at 6 months [20]
		  • Topical 5 % 5-FU applied for 9–16 weeks. Recurrence rates up to 50 %, initial responses in up to 90 % [14]
		• Photodynamic therapy
		• Surgical treatments:
		  • Wide-local excision (>1 cm margins). Surgical excision is recommended only if the lesion is <30 % of the anal circumference. Recurrence rates up to 63 % in 1 year
		• Ablative treatments:
		  • HRA with cautery ablation. Recurrence up to 79 % in 12 months in HIV+ patients.
		  • CO_2 laser ablation
		  • Cryotherapy
		• Radiotherapy in selected cases
			• High rate of recurrence with all the treatment options available. HRA every 4–6 months, and case-by-case analysis of re-treatment options is recommended	• Follow-up every 4–6 weeks

(continued)

(continued)

	Work-up	Treatment		Follow-up (F/U) (time after primary treatment)
		Primary	Recurrence	
AIN I or LGAIN	• Comprehensive history • Digital rectal examination • High-resolution anoscopy (HRA) with acetic acid 3 % and Lugol's iodine • Gynecological examination in women, with cervical cancer screening as appropriate	• Watchful waiting	• Usually have an indolent course, and a watchful waiting approach is recommended	• If HIV negative perform anoscopy every 12 months • If HIV positive anoscopy every 6 months. This subset of patients has a risk of progression to higher grades greater than 50 % at 2 years [23]

- Recurrence rates are high, usually between 20 and 68 % at 1 year with all therapies [19, 21, 22].
- A mapping procedure before surgery may decrease the incidence of positive margins and allow operative planning for defect closure. Up to 52 % may require skin grafts and 22 % rotational flaps [22].
- Mapping biopsies should be performed before any surgical treatment. Local excision should only be considered if lesions cover less than one-third of the anal circumference [24].
- If there are large lesions, excision of just the worst areas is possible, with continued observation of the adjacent areas [20].

AIN anal intraepithelial neoplasia, *HGAIN* high-grade AIN, *LGAIN* low-grade AIN, *HRA* high-resolution anoscopy

Anal canal carcinoma

Presentation	Prognosis 5-Year overall survival (OS)
• Localized (50 %)	80 %
• Regional (35 %)	60 %
• Metastatic (15 %)	5–15 %

Tumour size >5 cm, nodal and extra-pelvic metastases constitute the most important prognostic features influencing overall survival [25]. Tumour >5 cm and tumour invasion to other organs are frequently identified as risk factors for colostomy [25–27].

The rate of regional lymph node (LN) metastases is linked to the stage of the primary tumour. Synchronous inguinal node metastasis has been observed in 6 % of patients with T1 or T2 tumours and in 16 % of patients staged with T3 or T4 disease. Pelvic node metastases are found in approximately 20–25 % of patients at presentation.

The American Joint Committee on Cancer (AJCC) 7th edition is the current recommended anal cancer staging system. The AJCC classification applies to squamous cell carcinomas only; melanomas, carcinoid tumours, and sarcomas are not included.

Management

Anal Canal Carcinoma: Local/Regional Disease (Any T, Any N, M0)

	Work-up	Treatment		Follow-up (F/U) (time after primary treatment)
		Primary	Recurrence	
Early anal canal cancer (T1–T2, N0) Locally advanced or regional disease (T3–T4, N0 or any T N+)	• Comprehensive history • Digital rectal examination • Clinical assessment of inguinal lymph nodes (with FNAB if suspicious) • Anoscopy • Gynecological examination in women, with cervical screening as appropriate • Imaging: – CT thorax – CT abdomen and pelvis – Pelvic MRI	• The standard treatment is combined concurrent radiation and chemotherapy, delivered with 5-FU and MMC to the primary lesion and regional nodal basins (for N+ disease and for elective node irradiation) [28–32] • Cisplatin and 5-FU concurrent with RT and as induction chemotherapy had lower DFS and OS compared to concurrent RT, 5-FU, and MMC [25, 29, 33, 34] • Cisplatin and 5-FU concurrent with RT and as adjuvant chemotherapy showed no advantage over RT, 5-FU, and MMC [35] • The omission of MMC resulted in significantly higher local failure and colostomy rate than radiation with both 5-FU and MMC [32] • Primary surgical management should be reserved for select cases based on patient factors, and should follow a discussion at an MCC	• Local recurrence/persistence of disease: – Abdominoperineal or multivisceral [36] pelvic resection. R0 resection achieved in 62–91 % of cases; survival decreased in R1/R2 margins [36–40] – Most series describe a locoregional recurrence rate of 30–74 % following radical surgery [37, 38, 41–43] – 5-year survival after salvage surgery between 39–64 % [37, 40–44]. Local control and survival rates are strongly dependent on patient selection • Regional recurrence: – Inguinal LNs—recurrence rates <5 % in those who receive elective RT to inguinal regions – Formal groin dissection or consideration of inguinal irradiation (if the inguinal region has not received prior radiation therapy) +/− chemotherapy [23, 38, 42, 45, 46] • Distant metastases: – Chemotherapy regime assessed on case-by-case basis [8] – There is currently insufficient evidence to support metastasectomies. However, resection may be considered on individual case basis	• 4–8–12 weeks: – History and review of symptoms – Physical examination, including DRE • 12 weeks and subsequent assessments, if there is persistent or recurrent disease: – DRE – Biopsy – Restaging – Discussion for surgery • Every 3 months for 2 years: – History and review of symptoms – Physical examination including DRE – Anoscopy, if indicated. • At 3 months and every 6 months for 2 years: – CT chest/abdomen/pelvis – MRI if recommended by radiologist • Every 6 months from 2 to 3 years: – History and review of symptoms – Physical examination including DRE – Anoscopy if indicated • Annually from 3 to 5 years: – History and review of symptoms – Physical examination including DRE – Anoscopy if indicated

- Quality Indicators:
  - Ensure that the anal canal lesion is biopsy-proven squamous cell carcinoma prior to proceeding with comprehensive staging investigations.
  - Patients presenting with clinical or radiographic evidence of inguinal lymph node metastases should undergo pre-treatment FNA biopsy to confirm the diagnosis.
  - **Risk Factors:** Consider HIV testing if the patient has a known risk factor. HIV-positive patients should receive concomitant management of HIV infection by their primary care physician or infectious disease specialist.

MCC multidisciplinary cancer conference, *FNAB* fine-needle aspiration biopsy, *MMC* mitomycin C, *DRE* digital rectal examination

Special Notes

- **If there is persistent disease** on the **first clinical follow-up**, clinical reevaluation is warranted in 4 weeks to ensure full treatment effect. If there is further tumour regression or if tumour size is stable, continue close clinical surveillance monthly. If the tumour progresses or persists after 6 months, confirm the diagnosis with a biopsy, restage, and treat as treatment failure. If there is complete clinical remission at the time of assessment, biopsy is not indicated. Follow the proposed surveillance schedule provided above.
- Patients undergoing salvage surgery following previous pelvic RT experience a high rate of post-operative complications (37–72 %) particularly perineal infections and delayed wound healing [36, 37, 43, 44]. Consideration should be given to the use of a myocutaneous flap for perineal reconstruction [36, 37, 39, 40, 44].
- Induction chemotherapy with cisplatin and 5-FU is not supported in the literature; there was no benefit in overall, disease-free, or colostomy-free survival [17, 21, 22]. Similarly, the routine use of adjuvant chemotherapy with 5-FU and cisplatin is not supported [35].

Anal Canal Carcinoma: Metastatic (Any T Any N M+)

Work-up	Management
• Comprehensive history • Digital rectal examination • Clinical assessment of inguinal lymph nodes (with FNAB if suspicious) • Anoscopy • Gynecological examination in women, with cervical screening as appropriate • Imaging: – CT thorax – CT abdomen and pelvis – Pelvic MRI	• Chemotherapy regime assessed on case-by-case basis [8] • If the primary cancer and/or symptomatic regional node metastases are present, consider the addition of chemo-radiation or surgical excision for local control (as described for M0 disease)

FNAB fine-needle aspiration biopsy

Anal Margin/Perianal Carcinoma: Local/Regional Disease (Any T, Any N, M0)

	Work-up	Treatment		Follow-up (F/U) (time after primary treatment)
		Primary	Recurrence	
Well-differentiated cancer (T1, N0)	• Comprehensive history • Digital rectal examination • Clinical assessment of inguinal lymph nodes (with FNAB if suspicious) • Anoscopy • Gynecological examination in women, with cervical cancer screening as appropriate • Imaging: – CT thorax – CT abdomen and pelvis – Pelvic MRI	• Local excision with negative margins, provided that sphincter function is not compromised [7, 8, 31] • There is no agreement on what margin of resection constitutes an "adequate" margin, particularly with respect to the deep margin. In surgical planning, 1 cm margins are recommended [23, 47]. • If a margin has invasive cancer within 3 mm, and re-excision is not feasible, consider as "biopsy excision" and treat with chemo-radiation [23]. • If a margin has in situ cancer (high-grade dysplasia) at resection margin, observation at 3 monthly intervals for 2 years is a reasonable strategy [24]	• Local recurrence: – Consider salvage radiation combined with chemotherapy in patients initially treated with local excision – Consider abdominoperineal or multivisceral pelvic resection based on the pattern of local recurrence – Treatment decisions should be made on an individual case basis following a discussion at a Multidisciplinary Cancer Conference • Regional recurrence: – Inguinal LNs—Consideration of inguinal irradiation (if the inguinal region has not received prior radiation therapy) +/– chemotherapy or formal groin dissection (if radiation therapy was given consider flap reconstruction) [7, 8] • Distant Metastases: – Chemotherapy assessed on case-by-case basis [8] – There is currently insufficient evidence to support metastasectomies. However, resection may be considered on an individual case basis	• 4–8–12 weeks: – History and review of symptoms – DRE – Inguinal LN evaluation • Every 3 months for 2 years: – History and review of symptoms – DRE – Inguinal LN evaluation – Anoscopy if indicated – CT chest/abdomen/pelvis (except T1N0—at 6 months and then annually to 5 years) • Every 6 months from 2 to 3 years: – History and review of symptoms – DRE – Inguinal LN evaluation – Anoscopy if indicated • Annually from 3 to 5 years: – History and review of symptoms – Physical examination including DRE Anoscopy if indicated
Management of locally advanced or regional disease (T2–T4, N0 or Any T N+)		• Combination chemo-radiation therapy delivered with 5-FU and mitomycin C to primary lesion and inguinal nodal basins [7, 8, 28–32]		

(continued)

(continued)

- Quality Indicators:
  - Ensure that the perianal lesion is biopsy-proven squamous cell carcinoma prior to proceeding with comprehensive staging investigations.
  - Patients presenting with clinical or radiographic evidence of inguinal lymph node metastases should undergo pre-treatment FNA biopsy to confirm the diagnosis.
  - Consider HIV testing if the patient has a known risk factor. HIV-positive patients should receive concomitant management of HIV infection by their primary care physician or infectious disease specialist.
  - Patients with previous resection may be at a higher risk of chronic pain, stenosis, or delayed wound healing if another excision is performed [14].

LN lymph node, *FNAB* fine-needle aspiration biopsy, *DRE* digital rectal examination

Anal Margin/Perianal: Carcinoma: Metastatic (Any T Any N M+)

Work-up	Management
• Comprehensive history • Digital rectal examination • Clinical assessment of inguinal lymph nodes (with FNAB if suspicious) • Anoscopy • Gynecological examination in women with cervical screening as appropriate • Imaging: – CT thorax – CT abdomen and pelvis – Pelvic MRI	• Chemotherapy regime should be determined on case-by-case basis [8] • If the primary cancer and/or symptomatic regional node metastases are present, consider the addition of local treatment (as described for M0 disease)

FNAB fine-needle aspiration biopsy

Landmark :Trials

Topic	Study	Methods	Results
First use of CRT—preoperative	Nigro Protocol Nigro et al. [9]	• Case series • $N=3$ • Patients received 30 Gy/3 weeks, + 5-FU+MMC, followed by APR after 6 weeks	• Two patients had a complete pathologic response at time of APR • One patient refused surgery, but had a complete clinical response
Radical CRT	Cummings et al. [48]	• Case series • $N=6$ • Patients received 50 Gy/4 weeks + 5FU+ MMC, no surgery	• All patients had a complete clinical response • No local recurrence with 6–20-month follow-up
CRT Protocols	UKCCCR [28] 13-year update: Northover et al. [49]	• RCT • $N=585$ • RT alone vs. RT + 5-FU+ MMC (CRT)	• 3-, 5-, and 10-year local failure rate of 53.4 %, 57.1 %, and 59.1 % for RT vs. 29.7 %, 32.3 % and 33.8 % with CRT • No statistically significant difference in OS at 3 years (65 % for CRT vs. 58 % RT alone) • Following 12 years follow-up, CRT: – Reduced the risk of locoregional relapse, HR 0.46 (95 % CI: 0.35–0.60 $p<0.001$) – Decreased risk of relapsing or dying, HR 0.70 (95 % CI: 0.58–0.84 $p<0.001$) – Decreased risk of having a colostomy or death, HR 0.76 (95 % CI: 0.63–0.91, $p=0.004$) • Increased disease survival, HR 0.67 (95 % CI: 0.51–0.88, $p=0.004$) • After 12 years of follow-up OS trended to be statistically significant in favour of CRT, possibly due to a higher incidence of non-cancer-related deaths in the CRT arm
	Bartelink et al. [30]	• Multicentre RCT • $N=110$ • RT alone vs. RT +5-FU + MMC (CRT)	• Local failure at 5 years = 50 % with RT vs. 32 % for CRT ($p=0.02$) • 5-year colostomy-free rate—72 % for CRT vs. 40 % for RT alone • No difference in 5-year OS (54 % RT vs. 58 % CRT)
	Flam et al. [32]	• RCT • $N=291$ • RT+5-FU vs. RT +5-FU + MMC	• At 4 years, the MMC arm resulted in a lower colostomy rate (9 % vs. 22 %; $p=0.002$), reduced local failure (16 % vs. 34 %; $p=0.0008$), higher colostomy-free survival (71 % vs. 59 %; $p<0.05$), and higher DFS (73 % vs. 51 %; $p=0.0003$) • OS was similar in both arms
	RTOG 98-11 Protocol Ajani et al. [29] 5-year update: Gunderson et al. [33]	• RCT • $N=644$ • 324 patients RT + 5-FU + MMC vs. 320 patients ICT 5-FU + Cispt + RT	• The 5-year DFS rate was 68 % in the MMC-based group vs. 58 % Cispt-based group ($p=0.006$) • The 5-year OS rate was 78 % in the MMC-based group and 71 % in the Cispt-based group ($p=0.026$, HR 1.37, CI: 1.04–1.81) • The cumulative colostomy rate trended in favour of the MMC-based cohort (12 % vs. 17 %; $p=0.075$, HR 1.48, CI: 0.98–2.23)

	ACT II James et al. [26, 50]	• RCT • *N* = 940 • 4 arms – 5-FU + Cispt CRT + no maintenance CT – 5-FU + Cispt + maintenance CT (Cispt + 5-FU) – 5-FU + MMC CRT + no maintenance CT – 5-FU + MMC + maintenance CT (Cispt + 5-FU)	• No differences in complete response at 26 weeks in MMC vs. Cispt (90.5 % vs 89.6 %, absolute difference –0.9 %, 95 % CI–4.9 to 3.1, $p = 0.64$) • No difference in 3-year progression-free survival maintenance CT vs. no maintenance CT (74 % vs. 73 %, HR 0.95, 95 % CI 0.75–1.21, $p = 0.7$) • No difference in OS in maintenance CT vs. no main. CT (HR 1.07 CI 0.81–1.41 $p = 0.65$) and in MMC vs. Cispt (HR 1.05, 95 % CI 0.80–1.38, $p = 0.7$) • No difference in 3 years CFS (maintenance CT MMC 73 %, maintenance CT with Cispt 75 %, no maintenance CT MMC 75 %, and no maintenance CT with Cispt 72 %) • Colostomy risk factors: Low Hb at baseline, male gender and tumour >T3
Surgery	Schiller et al. [37]	• Retrospective review • *N* = 40 • Review of the role of salvage surgery after LR or persistent disease	• 83 % cases achieved R0 resection • 5-year OS: 39 % • 5-year DFS: 30 % • Post-operative mortality: 5 % • Complications: 72 % • Locoregional recurrence: 86 % • Distant recurrence: 48 %
	Akbari et al. [38]	• Retrospective review • *N* = 57 – 55 APR – 2 LAR • Review of the role of salvage surgery after LR or persistent disease	• 5-year OS: 33 % • 82 % cases had an R0 resection • Post-operative mortality: 1.62 % • Patients with recurrence: 56 %
	Eeson et al. [42]	• Retrospective review • *N* = 51 • Review of the role of salvage surgery after LR or persistent disease	• 63 % had an R0 resection • 5-year OS: 29 % • 5-year disease-free survival: 24.7 %

CRT chemoradiotherapy, *OS* overall survival, *APR* abdominoperineal resection, *RT* radiotherapy, *MCC* mitomycin C, *RCT* randomized controlled trial, *DFS* disease-free survival, *ICT* induction chemotherapy, *SDB*, standard dose RT boost, *HDB* high-dose boost

HIV Patients and MSM

Approximately 80–90 % of all HIV-infected patients have evidence of HPV infection of the anal region. The risk of them developing ACC is 30-fold higher than the general population [2]; MSM also have a 20-fold increase risk of developing ACC, and the risk is even higher for MSM who are HIV positive [17].

Patients with HIV infection who develop anal canal carcinoma tend to be younger than those in the general population who have anal cancer, and there are a higher proportion of male patients [51–55]. ACC is diagnosed typically approximately 10–12 years after the HIV diagnosis [51, 56].

There is some data that suggest that HIV/AIDS patients have a higher risk of not tolerating full-dose chemoradiotherapy [7, 56], but this is not a general finding. The usual recommendation is to treat those with HIV infection by usual protocols, and adjust chemotherapy and/or RT doses on a case-by-case basis. There are also some data suggesting decreased local control and/or survival from cancer in HIV-positive patients [52], a finding not shared by other reports [53–56].

Prevention

Vaccination is now being recommended for certain high-risk groups, as up to 80 % of anal cancers can be prevented with the quadrivalent HPV vaccine (HPV types 6, 11, 16, and 18) [8, 57].

The American Advisory Committee on Immunization Practices now recommends vaccination in boys and girls 11–12 years, females 13–26 years, and males 13–21 who have not been previously vaccinated. The American Academy of Pediatrics also recommends that MSM up to the age of 26 should be vaccinated [7, 58].

There is a lack of strong evidence to determine the best screening methodology (DRE or cytology), its frequency, and the population of patients who would benefit the most [19, 59–61].

Referring to Medical Oncology

1. All patients with a biopsy-proven diagnosis of anal canal carcinoma should be referred to medical oncology for consideration of primary combined-modality treatment.
2. All patients with a biopsy-proven diagnosis of perianal (anal margin) carcinoma not suitable for local excision should be referred to medical oncology for consideration of primary combined-modality treatment.

Referring to Radiation Oncology

1. All patients with a biopsy-proven diagnosis of anal canal carcinoma should be referred to radiation oncology for consideration of primary combined-modality treatment.
2. All patients with a biopsy-proven diagnosis of perianal (anal margin) carcinoma not suitable for local excision should be referred to radiation oncology for consideration of primary combined-modality treatment.

Referring to Multidisciplinary Cancer Conference

1. All patients with clinically suspected or biopsy proven persistent or recurrent anal carcinoma following primary combined-modality or surgical treatment should be discussed at a Multidisciplinary Cancer Conference (MCC).
2. Patients not suitable for combined-modality therapy as the primary treatment of an anal carcinoma (due to patient co-morbidities or tumour-related factors) should be discussed at an MCC, and considered for radical radiation alone or radical surgery (possibly with adjuvant preoperative or postoperative radiation with/without chemotherapy).
3. Patients presenting with metastatic disease should be discussed at MCC.
4. All patients with a biopsy-proven diagnosis of adenocarcinoma of the anal canal or margin should be discussed at MCC. Standard of care remains surgery +/– adjuvant chemo-radiation. Several small series (including the Toronto experience) have found that local control can be achieved in about 50 % of cases with adenocarcinomas, less than about 3 cm in size using combination chemo-radiation alone. Treatment plans should be individualized on a case-by-case basis.

Toronto Pearls

- For patients undergoing chemo-radiation the use of intensity modulated radiation therapy may be associated with less treatment toxicity and better quality of life [62].
- For patients undergoing radical salvage surgery, the use of a myocutaneous flap for perineal reconstruction is recommended.
- In order to achieve an R0 resection in locally advanced or recurrent disease, a multidisciplinary surgical team (including uro-oncology, plastic surgery, and/or orthopedic surgery) should be used in the context of multivisceral pelvic resections.

- HIV-positive patients should be managed by the same regimens of investigation and treatment as non-HIV-infected patients. The risk of excessive reaction to radiation and/or chemotherapy is low. Treatment should be adjusted on an individual basis based on toxicity and side effect profile.
- Previous pelvic radiation is a relative, but not an absolute, contraindication to radiation and chemotherapy for anal cancer. While prior radiation for prostate cancer generally prevents the use of further radiation, prior treatment for cervix or uterine cancer may not. All such patients should be referred to a radiation oncologist for assessment and discussed at an MCC.

References

1. Moore HG, Guillem JG. Anal neoplasms. Surg Clin North Am. 2002;82(6):1233–51.
2. Tong WW, Hillman RJ, Kelleher AD, Grulich AE, Carr A. Anal intraepithelial neoplasia and squamous cell carcinoma in HIV-infected adults. HIV Med. 2014;15(2):65–76.
3. Madeleine MM, Finch JL, Lynch CF, Goodman MT, Engels EA. HPV-related cancers after solid organ transplantation in the United States. Am J Transplant. 2013;13(12):3202–9.
4. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370(9581):59–67.
5. Chiao EY, Krown SE, Stier EA, Schrag D. A population-based analysis of temporal trends in the incidence of squamous anal canal cancer in relation to the HIV epidemic. J Acquir Immune Defic Syndr. 2005;40(4):451–5.
6. Dandapani SV, Eaton M, Thomas Jr CR, Pagnini PG. HIV- positive anal cancer: an update for the clinician. J Gastrointest Oncol. 2010;1(1):34–44.
7. He LB, Shao MY, Tan K, Xu X, Li JY. The effects of light on bleaching and tooth sensitivity during in-office vital bleaching: a systematic review and meta-analysis. J Dent. 2012;40(8):644–53.
8. Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. Radiotherapy Oncol. 2014;111(3):330–9.
9. Nigro ND, Vaitkevicius VK, Considine Jr B. Combined therapy for cancer of the anal canal: a preliminary report. Dis Colon Rectum. 1974;17(3):354–6.
10. Frisch M, Glimelius B, van den Brule AJ, Wohlfahrt J, Meijer CJ, Walboomers JM, et al. Sexually transmitted infection as a cause of anal cancer. N Engl J Med. 1997;337(19):1350–8.
11. Richardson H, Kelsall G, Tellier P, Voyer H, Abrahamowicz M, Ferenczy A, et al. The natural history of type-specific human papillomavirus infections in female university students. Cancer Epidemiol Biomarkers Prev. 2003;12(6):485–90.
12. Franco EL, Villa LL, Sobrinho JP, Prado JM, Rousseau MC, Desy M, et al. Epidemiology of acquisition and clearance of cervical human papillomavirus infection in women from a high-risk area for cervical cancer. J Infect Dis. 1999;180(5):1415–23.
13. Webb SP, Lee CS. Epidermoid cancer of the anal canal. Clin Colon Rectal Surg. 2011;24(3):142–8.
14. Osborne MC, Maykel J, Johnson EK, Steele SR. Anal squamous cell carcinoma: an evolution in disease and management. World J Gastroenterol. 2014;20(36):13052–9.
15. Daling JR, Madeleine MM, Johnson LG, Schwartz SM, Shera KA, Wurscher MA, et al. Human papillomavirus, smoking, and sexual practices in the etiology of anal cancer. Cancer. 2004;101(2):270–80.

16. Frisch M, Olsen JH, Bautz A, Melbye M. Benign anal lesions and the risk of anal cancer. N Engl J Med. 1994;331(5):300–2.
17. Machalek DA, Poynten M, Jin F, Fairley CK, Farnsworth A, Garland SM, et al. Anal human papillomavirus infection and associated neoplastic lesions in men who have sex with men: a systematic review and meta-analysis. Lancet Oncol. 2012;13(5):487–500.
18. Castor M, da Silva HJ, Gondim Martins DB, de Mello RJ. HPV and precancerous lesions of anal canal in women: systematic review. Int J Colorectal Dis. 2012;27(3):271–6.
19. Bejarano PA, Boutros M, Berho M. Anal squamous intraepithelial neoplasia. Gastroenterol Clin North Am. 2013;42(4):893–912.
20. Scholefield JH, Harris D, Radcliffe A. Guidelines for management of anal intraepithelial neoplasia. Colorectal Dis. 2011;13 Suppl 1:3–10.
21. Goldstone SE, Johnstone AA, Moshier EL. Long-term outcome of ablation of anal high-grade squamous intraepithelial lesions: recurrence and incidence of cancer. Dis Colon Rectum. 2014;57(3):316–23.
22. Margenthaler JA, Dietz DW, Mutch MG, Birnbaum EH, Kodner IJ, Fleshman JW. Outcomes, risk of other malignancies, and need for formal mapping procedures in patients with perianal Bowen's disease. Dis Colon Rectum. 2004;47(10):1655–60. discussion 60-1.
23. Steele SR, Varma MG, Melton GB, Ross HM, Rafferty JF, Buie WD, et al. Practice parameters for anal squamous neoplasms. Dis Colon Rectum. 2012;55(7):735–49.
24. Simpson JA, Scholefield JH. Diagnosis and management of anal intraepithelial neoplasia and anal cancer. BMJ. 2011;343:d6818.
25. Gunderson LL, Moughan J, Ajani JA, Pedersen JE, Winter KA, Benson 3rd AB, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US Gastrointestinal Intergroup RTOG 98-11 phase 3 trial. Int J Radiat Oncol Biol Phys. 2013;87(4):638–45.
26. Glynne-Jones R, Kadalayil L, Meadows HM, Cunningham D, Samuel L, Geh JI, et al. Tumour- and treatment-related colostomy rates following mitomycin C or cisplatin chemoradiation with or without maintenance chemotherapy in squamous cell carcinoma of the anus in the ACT II trialdagger. Ann Oncol. 2014;25(8):1616–22.
27. Bilimoria KY, Bentrem DJ, Rock CE, Stewart AK, Ko CY, Halverson A. Outcomes and prognostic factors for squamous-cell carcinoma of the anal canal: analysis of patients from the National Cancer Data Base. Dis Colon Rectum. 2009;52(4):624–31.
28. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. Lancet 1996;348(9034):1049–54.
29. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson 3rd AB, Thomas Jr CR, et al. Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA. 2008;299(16):1914–21.
30. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol. 1997;15(5):2040–9.
31. Spithoff K, Cummings B, Jonker D, Biagi J. Gastrointestinal Cancer Disease Site Group. Management of squamous cell cancer of the anal canal. Biagi J, Keshavarz, H Toronto (ON): Cancer Care Ontario; 2009 Mar 31 [endorsed 2013]. Program in Evidence-based Care Evidence-Based Series No.: 2-8 Version 2
32. Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol. 1996;14(9):2527–39.
33. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson 3rd AB, et al. Long-term update of US GI intergroup RTOG 98-11 phase III trial for anal carcinoma: survival,

relapse, and colostomy failure with concurrent chemoradiation involving fluorouracil/mitomycin versus fluorouracil/cisplatin. J Clin Oncol. 2012;30(35):4344–51.
34. Peiffert D, Tournier-Rangeard L, Gerard JP, Lemanski C, Francois E, Giovannini M, et al. Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. J Clin Oncol. 2012;30(16):1941–8.
35. James R, Meadows H, Wan S. ACT II: the second UK phase III anal cancer trial. Clin Oncol. 2005;17(5):364–6.
36. Tan KK, Pal S, Lee PJ, Rodwell L, Solomon MJ. Pelvic exenteration for recurrent squamous cell carcinoma of the pelvic organs arising from the cloaca--a single institution's experience over 16 years. Colorectal Dis. 2013;15(10):1227–31.
37. Schiller DE, Cummings BJ, Rai S, Le LW, Last L, Davey P, et al. Outcomes of salvage surgery for squamous cell carcinoma of the anal canal. Ann Surg Oncol. 2007;14(10):2780–9.
38. Akbari RP, Paty PB, Guillem JG, Weiser MR, Temple LK, Minsky BD, et al. Oncologic outcomes of salvage surgery for epidermoid carcinoma of the anus initially managed with combined modality therapy. Dis Colon Rectum. 2004;47(7):1136–44.
39. Sunesen KG, Buntzen S, Tei T, Lindegaard JC, Norgaard M, Laurberg S. Perineal healing and survival after anal cancer salvage surgery: 10-year experience with primary perineal reconstruction using the vertical rectus abdominis myocutaneous (VRAM) flap. Ann Surg Oncol. 2009;16(1):68–77.
40. Renehan AG, Saunders MP, Schofield PF, O'Dwyer ST. Patterns of local disease failure and outcome after salvage surgery in patients with anal cancer. Br J Surg. 2005;92(5):605–14.
41. Mullen JT, Rodriguez-Bigas MA, Chang GJ, Barcenas CH, Crane CH, Skibber JM, et al. Results of surgical salvage after failed chemoradiation therapy for epidermoid carcinoma of the anal canal. Ann Surg Oncol. 2007;14(2):478–83.
42. Eeson G, Foo M, Harrow S, McGregor G, Hay J. Outcomes of salvage surgery for epidermoid carcinoma of the anus following failed combined modality treatment. Am J Surg. 2011;201(5):628–33.
43. Nilsson PJ, Svensson C, Goldman S, Glimelius B. Salvage abdominoperineal resection in anal epidermoid cancer. Br J Surg. 2002;89(11):1425–9.
44. Harris DA, Williamson J, Davies M, Evans MD, Drew P, Beynon J, et al. Outcome of salvage surgery for anal squamous cell carcinoma. Colorectal Dis. 2013;15(8):968–73.
45. Blinde SE, Schasfoort R, Mens JW, Verhoef C, Olofsen M, Nuyttens JJ. Inguinal lymph node recurrence in the untreated groin of patients with anal carcinoma. Dis Colon Rectum. 2014;57(5):578–84.
46. Gerard JP, Chapet O, Samiei F, Morignat E, Isaac S, Paulin C, et al. Management of inguinal lymph node metastases in patients with carcinoma of the anal canal: experience in a series of 270 patients treated in Lyon and review of the literature. Cancer. 2001;92(1):77–84.
47. Skibber J, Rodriguez-Bigas MA, Gordon PH. Surgical considerations in anal cancer. Surg Oncol Clin N Am. 2004;13(2):321–38.
48. Cummings BJ, Harwood AR, Keane TJ, Thomas GM, Rider WD. Combined treatment of squamous cell carcinoma of the anal canal: radical radiation therapy with 5-fluorouracil and mitomycin-C, a preliminary report. Dis Colon Rectum. 1980;23(6):389–91.
49. Northover J, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). Br J Cancer. 2010;102(7):1123–8.
50. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 x 2 factorial trial. Lancet Oncol. 2013;14(6):516–24.
51. Nagle D. Anal squamous cell carcinoma in the HIV-positive patient. Clin colon Rectal Surg. 2009;22(2):102–6.
52. Oehler-Janne C, Huguet F, Provencher S, Seifert B, Negretti L, Riener MO, et al. HIV-specific differences in outcome of squamous cell carcinoma of the anal canal: a multicentric cohort

study of HIV-positive patients receiving highly active antiretroviral therapy. J Clin Oncol. 2008;26(15):2550–7.
53. Abramowitz L, Mathieu N, Roudot-Thoraval F, Lemarchand N, Bauer P, Hennequin C, et al. Epidermoid anal cancer prognosis comparison among HIV+ and HIV- patients. Aliment Pharmacol Ther. 2009;30(4):414–21.
54. Seo Y, Kinsella MT, Reynolds HL, Chipman G, Remick SC, Kinsella TJ. Outcomes of chemoradiotherapy with 5-Fluorouracil and mitomycin C for anal cancer in immunocompetent versus immunodeficient patients. Int J Radiat Oncol Biol Phys. 2009;75(1):143–9.
55. Chiao EY, Giordano TP, Richardson P, El-Serag HB. Human immunodeficiency virus-associated squamous cell cancer of the anus: epidemiology and outcomes in the highly active antiretroviral therapy era. J Clin Oncol. 2008;26(3):474–9.
56. Fraunholz I, Rabeneck D, Gerstein J, Jack K, Haberl A, Weiss C, et al. Concurrent chemoradiotherapy with 5-fluorouracil and mitomycin C for anal carcinoma: are there differences between HIV-positive and HIV-negative patients in the era of highly active antiretroviral therapy? Radiother Oncol. 2011;98(1):99–104.
57. Palefsky JM, Giuliano AR, Goldstone S, Moreira Jr ED, Aranda C, Jessen H, et al. HPV vaccine against anal HPV infection and anal intraepithelial neoplasia. N Engl J Med. 2011;365(17):1576–85.
58. Committee on Infectious D. HPV vaccine recommendations. Pediatrics. 2012;129(3):602–5.
59. Ong JJ, Chen M, Grulich AE, Fairley CK. Regional and national guideline recommendations for digital ano-rectal examination as a means for anal cancer screening in HIV positive men who have sex with men: a systematic review. BMC Cancer. 2014;14:557.
60. Health QO. Anal dysplasia screening: an evidence-based analysis. Ont Health Technol Assess Ser. 2007;7(4):1–43.
61. Smyczek P, Singh AE, Romanowski B. Anal intraepithelial neoplasia: review and recommendations for screening and management. Int J STD AIDS. 2013;24(11):843–51.
62. Han K, Cummings BJ, Lindsay P, Skliarenko J, Craig T, Le LW, et al. Prospective Evaluation of Acute Toxicity and Quality of Life After IMRT and Concurrent Chemotherapy for Anal Canal and Perianal Cancer. Int J Radiat Oncol Biol Phys. 2014;90(3):587–94.

Chapter 4
Breast Cancer

Dan Charleton, Jessica Maxwell, Amanda Roberts, Jean-François Boileau, Tulin Cil, Mark Corrigan, Claire Holloway, Ralph George, and David R. McCready

Introduction

Breast cancer is the most common cancer among Canadian women with the exception of non-melanoma skin cancer. An estimated 24,400 new cases occurred in Canada in 2014. Breast cancer is responsible for 26 % of all cancers in females and 14 % of all cancer-related deaths in females. 1 in every 9 women is expected to develop breast cancer during her lifetime and 1 in 30 women will die of breast cancer [1].

Dan Charleton, Jessica Maxwell and Amanda Roberts are the co-first authors.

D. Charleton, M.D., F.R.C.S.C. (✉) • J. Maxwell, M.D., F.R.C.S.C.
A. Roberts, M.D., M.P.H., F.R.C.S.C.
Fellow, Breast Surgery, University of Toronto, Toronto, ON, Canada
e-mail: dancharleton@gmail.com; 8Jem3@queensu.ca; amanda.roberts@mail.utoronto.ca

J.-F. Boileau, M.D., M.Sc., F.R.C.S.C.
Department of Surgery, Montreal Jewish General Hospital, Seagal Cancer Centre, Montreal, QC, Canada
e-mail: boileaujf@gmail.com

T. Cil, M.D., M.Ed., F.R.C.S.C. • C. Holloway, M.D., Ph.D., F.R.C.S.C.
R. George, M.D., Ph.D., F.R.C.S.C. • D.R. McCready, M.S., M.Sc., F.R.C.S.C., F.A.C.S.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: Tulin.Cil@wchospital.ca; Tulin.Cil@uhn.ca; claire.holloway@sunnybrook.ca; GeorgeR@smh.ca; David.McCready@uhn.ca

M. Corrigan, M.B., B.A.O., B.Ch., B.Med.S.C.I., M.D., F.R.C.S.I.
Department of Surgery, Cork University Hospital, Cork, Ireland
e-mail: markacorrigan@gmail.com; markanthonycorrigan@yahoo.com

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_4

Presentation	Prognosis 5-Year overall survival (OS)
• Early breast cancer[a] (75–80 %)	90–100 %
• Locally advanced breast cancer[a] (10–20 %)	36–67 %
• Distant metastasis (5 %)	26 %

[a]See definitions in the chapter

The recommended staging system is the 7th edition of American Joint Committee on Cancer (AJCC) [2].

The surgical management of breast cancer requires an understanding of the complete spectrum of breast pathology, both malignant and premalignant. As a result, an overview of this continuum is presented: from high-risk pathologies, through pre-invasive disease, to invasive disease and the management of some of its various subtypes.

Benign, but Worrisome

Within the pathological examination of breast tissue, there exist spectrums of conditions, which often bridge the divide between benign and malignant. They can present difficulty to the clinician, in terms of their appropriate management and—like many aspects of breast treatment—they are under constant review. Below we have summarised several of the more commonly encountered entities:

Entity	Definition and diagnosis	Treatment	Comments
Atypical ductal hyperplasia (ADH)	• A proliferation of uniform epithelial cells with monomorphic round nuclei filling part, but not all the involved duct • Diagnosis: no symptoms, incidental, often calcifications	• If found on CNB, the area should be removed to ensure that no adjacent carcinoma is present • If found at the margins of an excised lesion, re-excision is not generally considered necessary	• Atypical hyperplasia confers a substantial increase in the risk of subsequent breast cancer (RR 3.7–5.3) [3]
Atypical lobular hyperplasia (ALH)	• Monomorphic, evenly spaced, dyshesive cells filling part, but not all, of the involved lobule. ALH can also involve ducts • Diagnosis: no symptoms, incidental	• If found on CNB, the area should be removed to ensure that no adjacent carcinoma is present • If found at the margins of an excised lesion, re-excision is not generally considered necessary	• ALH is associated with an increased risk of both ipsilateral and contralateral breast cancer, with the Nurses' Health Study demonstrating that only 56 % of cancers developing in women with ALH occurred in the ipsilateral breast. The cumulative incidence of breast cancer over 30 years in patients with ALH approached 35 % [4]
Lobular carcinoma in situ (LCIS)	• Abnormal cell growth in the lobules of the breast that represents an increased risk of cancer rather than being a premalignant condition per se • Distinguish between classic (cLCIS) and pleomorphic (pLCIS) to plan treatment • Diagnosis: no symptoms, incidental	• If found on CNB, the area should be removed to ensure no adjacent carcinoma is present • If found at the margins of an excised lesion, re-excision is not generally considered necessary	• In a NSABP study of 180 women with LCIS, 5 % developed an ipsilateral invasive carcinoma after 12 years of follow-up, while a similar fraction (5.6 %) developed a contralateral invasive tumour [5] • Pleomorphic LCIS is an aggressive variant of LCIS, which is a newly categorised entity, often treated as DCIS sharing pathologic features with DCIS, and is often treated with excision to clear margins, similar to DCIS [6]
Intraductal papilloma	• Intraluminal epithelial fronds that can exhibit a variety of alterations from hyperplasia to carcinoma • Diagnosis: breast lump, nipple discharge (often bloody), or nodule on ultrasound or by ductoscopy	• Generally, the advice is for excision given the risk of malignancy. If the absence of atypia can be proven, however, there might be a role for observation	• Without atypia, the chance of malignancy is very small (<3 %), but with atypia, some authors have reported the associated rate of coexistent cancer to be as high as 67 % [7] – One of the largest multicentre series (n=238), reported an upgrade rate of 14.4 %, with only 3.7 % upgraded to invasive. Older age and presence of atypia on core biopsy were associated with risk of malignancy [8]
Sclerosing adenosis	• A benign condition, which involves the development of excessive tissue in the breast lobules • Diagnosis: occasional lump/nodules or pain, and occasional microcalcifications. Perform CNB	• After CNB, excision is only recommended in the following situations: – Limited sampling – Presence of atypia – Radiological discordance	• The risk of malignancy from sclerosing adenosis is linked to its potential to become ADH, ALH, LCIS, or DCIS, which has made some authors quote an increased risk of 1.5 times, above baseline risks of 1.5 times the normal risk [9]

(continued)

(continued)

Entity	Definition and diagnosis	Treatment	Comments
Microglandular adenosis	• A rare type of adenosis, resembling tubular carcinoma, where irregular clusters of small tubules are present in adipose or fibrous tissues • Diagnosis: may present as mass • Perform CNB	– Given risk of carcinoma, perform excision	– Microglandular adenosis is poorly studied, but is associated with a carcinoma rate of approximately 23 % [9, 10]
Radial scars and complex sclerosing lesions	• Benign, spiculated masses, characterised by a sclerotic-appearing (scar like) centre with peripheral entrapped normal breast ducts and lobules • Diagnosis: no symptoms. Perform imaging and CNB	• The standard management is to excise if detected as a mammographic lesion • However, if the diagnosis is made incidentally on a CNB and atypia is not identified, there may be a role for observation	• A large study looked at about 157 non-palpable lesions across 11 institutions. With atypia, the rate of cancer was 28 % but with no atypia, it was 4 % • Carcinoma was missed in 9 % of spring-loaded biopsy devices and in 0 % of vacuum-assisted biopsy devices. Carcinoma was also missed in 8 % of lesions sampled with less fewer than 12 specimens or more specimens [11]
Pseudoangiomatous stromal hyperplasia (PASH)	• Benign, stromal proliferation • More common in pre-menopausal women, possible hormonal etiology • Diagnosis: single, well-circumscribed, palpable mass	• If diagnosed conclusively on CNB, PASH can be managed expectantly • Excise if discordance with imaging or increase in size of lesion	• Although PASH is benign, recurrence after excision is reported in 15–22 % of cases
Flat epithelial atypia (FEA)	• A morphologically diverse group consisting of atypia within columnar cell change and hyperplasia • Diagnosis: no symptoms. Perform imaging and CNB	• The current standard of care is to excise lesions where FEA has been diagnosed on CNB • The current standard of care is surgical excision; however there is controversy regarding the management of pure FEA on CNB	• Retrospective data shows upgrade to DCIS or IDC in 9.5 % of pure FEA [12]. The data here is very poor, with a handful of retrospective studies • The largest prospective studies show an upgrade to carcinoma on surgical excision in 3.2 %–4.2 % in pure FEA [13, 14]. The upgrade rate increased to 18.6 % when ADH was present with FEA on original CNB [13] • Original small studies questioned the need to excise FEA following core biopsy [15]. The largest, albeit still quite small ($n=95$ pure FEA) [14] series, however, demonstrated a 9.5 % rate of finding of either invasive carcinoma (4.2 %) or DCIS (5.3 %) [11]

NSABP national surgical adjuvant breast and bowel project, *DCIS* ductal carcinoma in situ, *RR* relative risk, *FEA* flat epithelial atypia, *CNB* core needle biopsy

Ductal Carcinoma In Situ

Ductal carcinoma in situ (DCIS) is a pre-invasive breast cancer that does not penetrate the basement membrane. The incidence of DCIS markedly increased from 5.8 per 100,000 women in the 1970s to 32.5 per 100,000 women in 2004 and then reached a plateau [16]. Approximately 90 % are asymptomatic and not palpable, with the remainder presenting as a lump, discharge, or Paget's disease of the nipple.

Although evidence suggests that a significant amount of DCIS does not progress to invasive cancer, our inability to distinguish which will progress and which will not has led to an aggressive approach to all DCIS [17, 18].

The indications for lumpectomy vs. mastectomy are similar in DCIS as with invasive disease, with mastectomy indicated where:

1. Area of DCIS is large, relative to breast size.
2. Disease is multicentric.
3. Radiotherapy is contraindicated.
4. Clear margins cannot be obtained with breast conservation.

The lack of true randomised data regarding breast conservative surgery (BCS) and mastectomy for DCIS should be noted. The first indication that BCS—in conjunction with adjuvant radiotherapy—was acceptable treatment for DCIS came from a subset analysis of 78 patients in the NSABP B-06 [19]. Originally enrolled because of presumed invasive breast cancer, these women were downgraded to DCIS on pathologic reanalysis. The local recurrence rate was 9 % in those that underwent radiotherapy vs. 43 % in those that did not. Retrospective studies have since confirmed that BCS provides survival rates similar to mastectomy; however local recurrence is higher, even with radiotherapy [20].

As mentioned, similar to invasive disease, there is good evidence for radiotherapy following a breast-conserving approach:

Study	Methods	Results
NSABP-B17 Fisher et al. [21]	• *N* = 818 • RCT • Patients assigned to lumpectomy alone vs. lumpectomy and RT	• At 7.5 years, RT reduced the incidence of ipsilateral invasive disease (13.4 % to 3.9 %) as well as ipsilateral DCIS (13.4 % to 8.2 %) • A subset analysis from this study also demonstrated that comedo necrosis was a risk factor for recurrence
EORTC 10853 Julien et al. [22]	• *N* = 1010 • RCT • Patients with DCIS and BCS randomised to receive no further treatment or RT	• RT reduced overall non-invasive recurrence at 10.5 years by 48 % and invasive recurrence by 42 %
UK/ANZ DCIS Cuzick et al. [23]	• *N* = 1701 • RCT • Patients with excised DCIS randomised to receive RT, tamoxifen, both or none	• RT reduced ipsilateral invasive recurrence at 12.7 years by 68 % and DCIS by 62 %, but with no effect on contralateral breast cancer

RCT randomised controlled trial, *HR* hazard ratio, *RT* radiotherapy

It is worth noting that both NSABP B-17 [21] and EORTC 10853 [22] came under some criticism for not providing mammographic correlation with the specimen or pre-operative evaluation and in NSABP B-17 [21] sampling of the surgical specimen was unable to exclude invasive disease or involved margins. This questioned the completeness of excision in both studies. As a result, many believe that this strengthens the argument for complete surgical resection rather than an approach that relies on radiotherapy as a means of dealing with residual disease.

There is some evidence, however, that radiotherapy may be safely omitted in some cases of DCIS:

1. Tumour less than 1.5 cm
2. Margins greater than 10 mm
3. Non-high grade, without necrosis (nuclear grade 1 or 2)
4. Patient age over 60 [24]

The EORTC 10853 [22] study demonstrated a recurrence rate of less than 4 % at 5 years of low-grade DCIS, making an argument for the omission of radiotherapy in this circumstance. More recently, a prospective study of 670 patients [25] demonstrated a 5-year recurrence of 15 % for high-grade DCIS, but only 6 % for low- or intermediate-grade DCIS, when excised with a minimum of 3 mm margins. However, the authors note an increase in recurrences beyond 5 years for all grades of DCIS and urge caution in applying these results to clinical practice. Another prospective trial of wide excision alone for low-to-intermediate-grade DCIS found an unacceptably high local recurrence rate of 12 % at 5 years and 15.6 % at 10 years [26].

Given the difficulty in determining which patients DCIS may be safely treated with wide excision alone, it remains the standard of practice at the University of Toronto to offer radiation to all patients having undergone breast-conserving surgery (BCS) for DCIS.

DCIS Recurrence

Approximately 25–50 % of recurrences are invasive disease. Factors involved in recurrence include:

1. Margin status
2. High-grade/comedo necrosis
3. Histological type and architecture
4. Age at diagnosis

Margin status has three times the power of tumour grade at predicting local recurrence [20]. The NSABP-B17 [21], NSABP-B24 [27] and EORTC clinical trials [22] have all revealed that clear margins significantly decrease recurrence.

No trials, however, have rigorously examined the optimum excision width. An analysis of pooled data from both randomised and non-randomised studies in 2009 concluded that a margin of 2 mm when excising DCIS was as safe as a larger margin when followed by radiotherapy [28]. Contributing to the debate is another meta-analysis, published in 2012, which showed a statistically significant decrease in recurrence for 10 mm margins compared to 2 mm margins (OR = 0.46; 95 % CI = 0.29–0.69) [29].

Although a high-grade lesion was originally thought to be a risk factor for recurrence, a 2006 review of the EORTC data [22] with a 10-year follow-up suggested that this may not be the case. It has, however, confirmed that comedo necrosis is an independent risk factor for recurrence, with 3 of 10 patients recurring by 10 years [22].

Age is also a significant factor in DCIS recurrence. The EORTC trial [22] demonstrated a higher recurrence rate in young women under 40, quoting a hazard ratio (HR) of 2.54 [22]. Similarly, the NSABP B-24 [27] trial found that the rate of ipsilateral cancer in women under 49 was 33/1000 women years as opposed to 13/1000 for those over 49 [30].

The management of recurrence is largely dependent on whether radiotherapy has been administered. If not, then a local resection may be possible; otherwise a mastectomy should be offered. There has been some suggestion that repeat resection and irradiation may be safe in the setting of recurrence. The data, however, is limited by short follow-up and is largely confined to the setting of invasive disease rather than DCIS [31] and this approach is, therefore, not universally accepted.

DCIS and the Axilla

The incidence of axillary metastases in DCIS is <1 % and these are likely to represent missed invasive disease, rather than true DCIS metastases. It should be borne in mind that the majority of reported sentinel lymph node (SLN) involvement in DCIS is revealed by immunohistochemical (IHC) techniques as isolated tumour cells or micrometastases, and the clinical significance of these is uncertain even in true invasive disease [32].

A joint committee of the American College of Surgeons, American College of Radiology and the College of American Pathologist recommended that axillary staging in patients with DCIS treated by BCS be reserved for those with invasive disease. For those undergoing mastectomy for DCIS, sentinel lymph node biopsy (SLNB) was recommended. This recommendation is made with a view to avoid axillary lymph dissection in the event of an upgrade from DCIS to invasive carcinoma on final pathology of the mastectomy specimen, as SLNB is not possible after mastectomy.

Invasive Breast Cancer

In this section, the management of invasive breast cancer is discussed, focusing on tumours less than 5 cm with no evidence of matted or fixed axillary lymph nodes, corresponding to T0, T1, T2 and N0, N1 (stages 0, I, IIA and IIB).

Work-up	Surgical management	Follow-up (F/U)
• History and physical exam • Imaging: – Review bilateral mammogram and ultrasound (assess for multifocal/multicentric disease, as well as contralateral disease) – Axillary US – Breast MRI if indicated (see below) • Core needle biopsy to confirm the diagnosis • Apply clip if neoadjuvant therapy is considered • CCO staging recommendations [33]: – Routine bone scanning, liver ultrasonography and chest radiography are not indicated before surgery • Post-operatively: – In women with stage I tumours, routine bone scanning, liver ultrasonography and chest radiography are not indicated as part of baseline staging – In women who have pathological stage II tumours, a postoperative bone scan is recommended as part of baseline staging – In women who have pathological stage III tumours, bone scan, chest radiography and liver ultrasound are recommended post-operatively	• Breast (local): – Breast-conservative surgery plus breast irradiation or mastectomy +/− post-mastectomy radiation therapy [34] • Axilla (regional): – Sentinel lymph node biopsy for clinical N0 patients – Axillary lymph node dissection for clinical N1 • Consider and discuss neoadjuvant chemotherapy in the following cases: – Triple-negative – Young patients (<40) – Her2/neu + – Reducing the size of tumour to facilitate BCS – Node-positive patients	• Regular clinical breast exam • Mammogram every 12 months

BCS breast-conserving surgery, *MRI* magnetic resonance imaging, *CCO* Cancer Care Ontario

Special Notes

- It is standard of care to obtain the diagnosis of invasive breast cancer with core needle biopsy. While the primary use of core needle biopsy is to establish a diagnosis, it is also useful in providing receptor status if neoadjuvant chemotherapy is considered. Furthermore, positive margin rates and the need for reoperation are reduced in women who have been assessed with core needle biopsy preoperatively [35].
- In breast cancer of a more advanced stage, Cancer Care Ontario has recommended that in women with pathological stage III tumours, bone scanning, liver ultraso-

nography or CT abdomen and chest radiography are recommended post-operatively as part of baseline staging. However, in women for whom treatment options are restricted to tamoxifen or hormone therapy, or for whom no further treatment is indicated because of age or other factors, routine bone scanning, liver ultrasonography and chest radiography are not indicated as part of baseline staging [33].

- Mammography remains the mainstay of breast imaging. MRI of the breast is considered an adjunct to mammography. Pre-operative diagnostic MRI detects additional ipsilateral lesions in up to 32 % of patients and contralateral lesions in 7 % of patients. Sensitivity ranges from 75 to 100 % and specificity from 80 to 100 % [35]. However, several studies have failed to show a decreased rate of positive margins in BCS for patients undergoing MRI [37, 38] while also showing an increased likelihood of mastectomy in such patients [38].
- According to the American College of Radiology, current indications for diagnostic MRI are:
  - Axillary adenocarcinoma with unknown primary
  - Evaluation of response to neoadjuvant chemotherapy
  - Assessment of extent of DCIS and IDC
  - Assessment of invasion of deep fascia
  - Evaluation of possible recurrence
- Diagnostic MRI can also be considered in patients with invasive lobular carcinoma, as there is some evidence that MRI reduces the need for re-excision surgery in this subset of patients, but at the cost of an increased likelihood of upfront mastectomy [38].

Breast-Conserving Surgery

The aim of breast conservation is to achieve a balance between complete resection of the tumour with negative margins and preservation of as much normal breast tissue as possible. Volume loss is the major determinant of cosmesis after BCS. A good cosmetic outcome maximises the psychosocial benefits of breast preservation [39].

In patients with no contraindication to BCS, there are several points to be discussed with the patient	BCS includes the lumpectomy to a negative margin, margin revision being necessary in about 20 % of cases If the margin is positive after appropriate attempts at therapeutic breast-conserving surgery, the patient should be considered for mastectomy
	BCS for DCIS and IDC includes administration of radiotherapy
	When compared with mastectomy, BCS may have a slightly higher risk of local recurrence. Both approaches, however, have equivalent survival outcomes

Absolute Contraindications to BCS

1. Early pregnancy, if radiation deemed necessary to be performed during pregnancy.
2. Multicentric IDC—diffuse-appearing suspicious 19 % microcalcifications or inability to resect the evident disease with acceptable cosmetic results.
3. Any contraindication to radiation therapy (e.g. active collagen vascular disease with severe vasculitis, ataxia telangiectasia).

Relative Contraindications to BCS

1. A history of collagen vascular disease, in remission.
2. Large tumour size in relation to the breast size.
3. A history of prior therapeutic irradiation to the breast region.

For invasive cancer, another consideration in the choice of surgical treatment of the primary tumour is the management of the axilla after positive SLNB. The ACOSOG Z0011 trial—detailed in section IV of this chapter—supports omission of axillary lymph node dissection (ALND) after positive SLNB in many patients treated with BCS. However, patients treated with mastectomy were excluded and the current standard remains completion of ALND in those cases. This may factor into the decision-making process for the patient and surgeon.

Trials for BCS vs. Mastectomy

Study	Methods	Results
NSABP-B06 Fisher et al. [31]	• *N* = 1851 • RCT • Patients in stages I and II were assigned total mastectomy/ALND, lumpectomy/ALND alone or lumpectomy/ALND + breast irradiation • Margins—no cancer cell at the surgical margin	• Follow-up—20 years • No significant differences in disease-free survival and overall survival • Recurrence rate in the ipsilateral breast was 14.3 % in the lumpectomy/ALND plus breast irradiation group and 39.2 % in the lumpectomy/ALND-alone group
Milan Group Veronesi et al. [32]	• *N* = 701 • RCT • Patients with tumour <2 cm were assigned radical mastectomy vs. quadrantectomy/ALND + radiotherapy • Margins—1.5–2.0 cm, with the overlying skin and deep fascia	• Follow-up—20 years • No statistical difference in overall survival • Recurrence rate higher in the BCS group (8.8 % vs. 2.3 %)

RCT randomised controlled trial

Meta-Analysis to Assess Surgical Margins in BCS for Early Breast Cancer

Study	Methods	Results
Houssami et al. [39]	• 33 studies • *N* = 28,162 patients (1506 with LR) • Impact of surgical margins on LR • Model 1—effect of margin status in relation to LR • Model 2—effect of margin distance to LR (1 mm vs. 2 mm vs. 5 mm)	• Higher probability of LR associated with positive/close margins vs. negative margins (OR 1.97) • No difference in LR with 1 mm vs. 2 mm vs. 5 mm margin distance • Wider margins unlikely to increase long-term local control

LR local recurrence, *OR* odds ratio

This work by Houssami et al. formed the basis of the Society of Surgical Oncology-American Society for Radiation Oncology (SSO-ASTRO) consensus guidelines for breast-conserving surgery for early-stage breast cancer. Using this data, a multidisciplinary panel concluded that "no ink on tumour" should be adopted as the standard for an adequate margin for invasive breast cancer [39]; this guideline has since been endorsed by the American Society of Clinical Oncology (ASCO) and the American Society of Breast Surgeons (ASBS) [41].

The Axilla

Management of the axilla is arguably the most controversial aspect of the breast cancer treatment paradigm. From considering axillary lymph node dissection (ALND) as the standard of care for all breast cancer patients, to now omitting patients with proven axillary metastases from further surgery, it is a complex facet of the management of invasive breast cancer.

Authors such as Steele et al. [42] in the 1980s challenged the belief that all breast cancer patients should have an ALND. They endorsed a system of axillary node sampling, whereby four nodes were "cherry picked" from level one of the axilla, and if negative for disease, no further surgery was performed. This limited axillary node sampling may be seen as the grandfather of SLNB, a technique which has supplanted ALND as the standard of care in staging the clinically negative axilla.

Several key trials have demonstrated the efficacy of SLNB

Study	Methods	Results
Multicenter Validation Study Krag et al. [43]	• $N=443$ • All patients underwent both SLNB and then ALND	• It demonstrated that this technique could be used by surgeons • At least 1 SLN was identified in 98 % of cases and the predictive value of a negative SLN was 96 %, with a false-negative rate of 11 %
ASCO Review Lyman et al. [44]	• $N=8059$ • Systematic review of 69 SLNB trials	• SLN identification was successful in 95 % of patients • The false-negative rate was 7.3 % (range 0–29 %). Using both radiocolloid and blue dye was more successful than blue dye alone
ALMANAC Mansel et al. [45]	• $N=1031$ • RCT • Patients randomly assigned to ALND vs. SLNB with delayed ALND if SLN positive	• SLNB group had less arm morbidity • SLNB group had better quality of life and arm functioning scores

(continued)

(continued)

Study	Methods	Results
NSABP B-32 Krag et al. [46]	• $N=5611$ • RCT • Comparing SLNB, followed by ALND vs. SLNB, followed by ALND for positive SLN	• Lymphatic mapping was successful in 97 %, and the false-negative rate was 9.8 % • No significant differences were observed in regional control or survival between the groups at follow-up of 8 years

ASCO American Society of Clinical Oncology, *SLN* sentinel lymph node, *SLNB* sentinel lymph node biopsy, *RCT* randomised controlled trial, *ALND* axillary lymph node dissection

Sentinel Lymph Node Biopsy and Axillary Dissection

The contribution of ALND to survival in women with breast cancer has been questioned since the publication of the NSABP B-04 [47] trial. It has often been the basis of argument against mandatory ALND. In this study, clinically node-negative patients were randomised to radical mastectomy (RM), total mastectomy (TM) plus axillary irradiation or TM alone. Forty percent of the RM group had lymph node involvement. However, axillary recurrence, as a first failure, was only in the TM-alone group. Moreover, the three groups had a similar overall survival [49]. In the era of SLNB, the contribution of axillary dissection to survival was revisited in the ACOSOG Z0011 trial [50]. In this prospective randomised non-inferiority trial, breast cancer patients receiving breast-conserving therapy with only one or two positive SLNs and with no gross extracapsular extension were randomised to SNLB-alone vs. ALND groups. The main criticism of this study is that it is underpowered, with a relatively short follow-up (median: 6.3 years) period. The overall survival and the disease-free survival of the SLNB-alone group appeared to be non-inferior to the ALND group.

The conclusions of the Z0011 trial are supported by another randomised non-inferiority trial (IBCSG 23-01). Patients with tumour size less than 5 cm and one or more micrometastatic sentinel lymph node were randomised to completion axillary dissection ($n=465$) or no further axillary surgery ($n=469$). In both groups, 9 % of patients received mastectomy for the primary tumour, unlike the Z011 trial. In those randomised to completion axillary dissection, there was a significantly higher rate of sensory neuropathy, motor neuropathy and lymphedema; 13 % had at least one additional lymph node involved. There was no significant difference in 5-year disease-free survival (84.4 % in the group with axillary dissection vs. 87.8 % in the group without) or cumulative incidence of breast cancer events (10.6 % in the group with axillary dissection vs. 10.8 % in the group without).

Studies in support of ALND *after positive SLNB*

Study	Methods	Results
Meta-Analysis Orr, 1999 [51]	• 6 RTCs • *N* = 3000 • Patients assigned to ALND or no ALND	• Limited by very few T1a tumours, no women over 70 years, no adjuvant treatment and a timeline of 1951–1987 • Demonstrated an improvement in absolute survival with ALND (range 4–16 %) using Bayesian statistics
SEER Database Analysis Joslyn, 2002 [52]	• Retrospective review • *N* = 257,157 • Women diagnosed with breast cancer in the SEER database between 1988 and 2000	• Women undergoing ALND had an increased survival • Also, with an increasing ratio of positive nodes to total number removed, there was a consistent trend towards reduced survival
Truong et al. [53]	• Retrospective population-based cohort • *N* = 8038 • Patients treated for T1–2 breast cancer in British Columbia between 1989 and 1998	• Overall and cancer-specific 5-year survival rates were significantly worse in those who had not undergone ALND (68 % vs. 85 % and 86 % vs. 91 %, respectively). Note that the much larger difference in overall survival suggests large heterogeneity between groups
Early Breast Cancer Trialists' Collaborative Group Analysis Clarke et al. [52]	• 78 RCTs • *N* = 42,000 • Comparing the effect of different types of local treatment on recurrence and survival	• While not directly examining ALND, the study showed that local control affects overall survival, a fact which is often used in support of ALND • Local recurrence positively impacted on the 15-year survival

RCT randomised controlled trials, *ALND* axillary lymph node dissection, *SEER* surveillance epidemiology and end results (US National Cancer Institute)

Studies in support of ALND omission *after positive SLNB*

Study	Methods	Results
NSABP B-04 Fisher et al. [55]	• *N* = 1843 • RCT • Women were assigned to radical mastectomy vs. simple mastectomy plus local nodal irradiation, or simple mastectomy with ALND delayed if needed	• This study is criticised for being underpowered and also for including many women with simple mastectomy who had some nodes removed with the breast specimen • There was no effect on survival of prophylactic ALND vs. nodal radiotherapy vs. no initial axillary treatment

(continued)

(continued)

Study	Methods	Results
The Breast Carcinoma Collaborative Group of the Institut Curie Cabanes et al. [56]	• *N* = 658 • RCT • Patients assigned to lumpectomy alone or lumpectomy plus ALND • All received RT, and women with positive LNs received chemotherapy	• Initially, ALND was associated with significantly better 5-year survival (97 % vs. 93 %) • However, after the data was reviewed with longer follow-up of 10–15 years, survival rates were similar (approximately 75 %) • The instance of regional recurrence was lower in women who had ALND. The results however were skewed, as the only women to receive chemotherapy were in the ALND group
Systematic Review and Meta-Analysis Sanghani et al. [57]	• 3 RCTs • Comparing ALND vs. no ALND (2000 and 2007) and a 4th trial comparing axillary radiotherapy vs. no axillary therapy	• No difference in overall survival or recurrence with axillary treatment • It is felt that the widespread use of adjuvant radiotherapy and chemotherapy contributed to these results
Z0011 Guiliano et al. [50]	• *N* = 891 • RCT • ALND vs. no ALND for women with positive SLNB	• At median follow-up of 6.3 years, the 5-year overall survival was 91.8 % in ALND and 92.5 % in those with SLNB. Importantly, disease-free survival was also similar with 82.2 % in ALND and 83.9 % with SLNB • It is criticised for its low numbers and an approximately 20 % lost to follow-up rate (unlike NSABP-B32 <1 %) • Powered for 1900 patients but closed earlier due to lower than expected mortality rate

RCT randomised controlled trials, *ALND* axillary lymph node dissection, *LN* lymph node, *SLNB* sentinel lymph node biopsy, *RT* radiotherapy

Special Notes

- Although by no means an exhaustive examination of the literature, the above studies do help demonstrate the controversy surrounding ALND. It should be always remembered that with the rapid changes in adjuvant therapy for breast cancer, one must examine the older literature with a certain degree of care. Certainly, it seems that the benefit of extensive axillary surgery is questionable in this era of effective adjuvant therapy. Given the limitations of the Z0011 study, however, it is difficult at the present time to completely advocate a definitive move away from the procedure.

- At the University of Toronto, we forego axillary dissection in patients meeting the Z011 inclusion criteria.

Management of Macrometastatic Axillary Disease

The Z0011 study results were practice changing and incorporated quickly into management guidelines (i.e. national comprehensive cancer network). Two recent studies, AMAROS and MA20, have contributed to the discussion regarding the axillary management of pathologically macrometastatic positive SLNs. These two trials are summarised below:

Study	Methods	Results
AMAROS Donker et al. [58]	• $N=4806 \rightarrow 1425$ (29.7 %) found to have +ve SLNB • RCT, non-inferiority trial • From 2001 to 2010, patients with cT1–2N0 invasive breast cancer were enrolled in the EORTC phase III non-inferiority AMAROS trial. Patients with previous neoadjuvant systemic treatment were excluded from the study • Patients were randomised to ALND or ART prior to SLNB and breast-conserving surgery or mastectomy. Patients with positive SLNs were then included in analysis. ART included radiation to level I, II, III and supraclavicular lymph nodes • Primary endpoint was 5-year axillary recurrence rate	• 5-year axillary recurrence was 0.43 % after axillary lymph node dissection and 1.19 % after axillary radiotherapy. Due to the unexpectedly low number of events, the non-inferiority test was underpowered and did not meet non-inferiority criteria. The axillary recurrence rate for patients with a negative sentinel node biopsy was 0.72 % (25 out of 3131 patients) during the entire follow-up period (median 6.1 year) • Clinical signs of lymphedema were noted more often following ALND than ART, 23 % versus 11 % at 5 years ($p<0.0001$). Rates of subjectively measured lymphedema were not different between groups. Range of motion and quality of life measurements were not significantly different between the two groups

(continued)

Study	Methods	Results
MA 20 Whelan et al. (abstract) [59]	• $N=1832$ • RCT • Women with high-risk node-negative or node-positive breast cancer treated with BCS and adjuvant chemotherapy and/or endocrine therapy were randomised to WBI (50 Gy in 25 fractions +/– boost irradiation) or WBI plus RNI (45 Gy in 25 fractions) to the internal mammary, supraclavicular and high axillary lymph nodes. The primary outcome was OS	• Overall 5-year survival: 90.7 % (WBI) vs. 92.3 % (RNI) non-significant difference, trend only, $p=0.07$ • Locoregional recurrence: 94.%% (WBI) vs. 96.8 % (RNI), $p=0.02$ • 5-year DFS: 84 % (WBI) vs. 89.7 % (RNI), $p=0.003$ • Toxicities: Pneumonitis 0.2 % (WBI) vs. 1.3 % (RNI) and lymphedema 4.1 % (WBI) vs. 7.3 % (RNI)

EORTC European Organisation for Research and Treatment of Cancer, *AMAROS* the after-mapping of the axilla: radiotherapy or surgery?, *ART* axillary radiation therapy, *RCT* randomised control trial, *BCS* breast-conserving surgery, *WBI* whole-breast irradiation, *RNI* regional nodal irradiation, *OS* overall survival

Isolated Tumour Cells and Micrometastases

Isolated tumour cells (ITCs)	Micrometastases
• Defined by the 7th edition of AJCC as "small clusters of cells not greater than 0.2 mm, or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section are classified as isolated tumour cells" [2] (pN0(i+)) • No further surgery, radiotherapy or chemotherapy is indicated by their presence	• Defined by a separate designation of pN1mi (>0.2 mm and no greater than 2.0 mm) to indicate micrometastases alone [2] • Although larger than ITCs, their clinical significance is also questionable: NSABP B-32 showed a 1.2 % lower 5-year survival in patients with micrometastases, compared to those that were pathologically node negative [46]

Special Notes

- The literature is populated by much discussion regarding the significance of isolated tumour cells (ITCs) and micrometastases. This debate has been largely superseded by the publication of Z0011 and its findings relating to the significance of macrometastases [50], along with Weaver et al. who demonstrated statistical, but no clinical significance to their presence [32].

Summary: Management of the Clinically Node-Negative Axilla

- SLNs are pathologically negative or contain only ITCs:
  - SLNB is the standard for staging and axillary surgery [60].

- SLNs contain micrometastatic disease on pathologic examination:
  - SLNB alone can safely manage burden of disease. However case should be discussed at Multidisciplinary Cancer Conference (MCC) to determine if identification of macrometastases will alter adjuvant therapy recommendations. If so, completion ALND may be considered [60].
- SLNs contain macrometastatic disease on pathologic examination:
  - If meets all inclusion criteria for Z0011 (T1 or T2 tumour, 1 or 2 positive SLNs, no gross extranodal extension, breast-conserving therapy, whole-breast radiotherapy planned, no neoadjuvant chemotherapy), no further ALND is required [60].

    If three or more positive SLNs and/or gross extranodal disease, consider completion ALND [60].
  - If patient has undergone mastectomy, consider completion ALND [60]. However, may discuss at MCC to review benefits/risks of completion ALND vs. axillary radiotherapy.

Locally Advanced Breast Cancer

Locally advanced breast cancer (LABC) is a heterogeneous entity. The term includes T3: tumours greater than 5 cm in maximum diameter, T4: tumours that directly invade skin or chest wall, as well as inflammatory breast cancer, and tumours that have extensive regional lymph node involvement (matted ipsilateral lymph nodes N2–N3) without evidence of distant metastatic disease at initial presentation. These tumours fall into the category of stage IIB and III disease as per AJCC 7th edition staging. It is clinically useful to separate LABC into operable and inoperable, or situations in which upfront surgery is of questionable overall benefit. Approximately 25–30 % of LABC are inoperable on presentation. Up to 20 % of patients with clinically LABC are metastatic after staging [61]. Signs of questionable operable benefit or inoperability include [62]:

1. Extensive skin edema
2. Satellite nodule in the skin
3. Inflammatory breast cancer
4. Involvement of supraclavicular or internal mammary lymph nodes
5. Pre-operative upper limb edema
6. Skin ulceration
7. Fixation to the chest wall
8. Fixed, matted ALN

Optimal management of LABC requires multimodality treatment. The usual order of treatment varies according to the patient and the tumour clinical stage and characteristics:

Work-up	Inoperable LABC	Operable LABC	Follow-up (F/U)
• Obtain the ER, PR and HER2/neu status • Imaging: – Breast MRI – CT scan chest, abdomen and pelvis – Bone scan • Apply a radiologic marker pre-initiation of chemotherapy • Precise tumour measurement and documentation of skin changes. • Record tumour site with transparent film or skin tattoo. • Consider discussion in MCC	• Neoadjuvant chemotherapy and reassess response after each cycle • If response—continue until completion of planned treatment or maximal response—then surgical management • If no response—discuss again in MCC. Options: – Alternate systemic therapy regimen – If operable: Surgical management – If non-operable: radiotherapy +/− planned surgical treatment	• Consider neoadjuvant chemotherapy in: – Any patient who will need adjuvant chemotherapy [63] and in whom surgical pathology information is not required to determine regimen – High-grade tumours [64] – HER2+ [64] – Triple negative (ER/PR/HER2$^-$) [65] – Young patients <35 years [66] – Patient has large tumour and seeks breast conservation – Patients with node-positive disease • Surgical management of the breast (usually mastectomy unless downstaging) and axilla (see below: SLNB vs. axillary dissection)	• Regular clinical breast exam • Mammogram every 12 months

ER estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *MCC* Multidisciplinary Cancer Conferences, *SLNB* sentinel lymph node biopsy

Special Notes

- Radiation therapy will be recommended post-mastectomy or post-BCS to patients with LABC
- Advantages of neoadjuvant chemotherapy:
  - Evaluation of in vivo response to chemotherapy
  - Downstaging to facilitate breast conservation

    Conversion from mastectomy to BCT occurs in approximately 23 % of patients [65]

    Local recurrence rates in this conversion group are slightly higher than in the mastectomy group (10.7 % vs. 7.6 %) [68]
  - Early introduction of chemotherapy to treat occult potential systemic metastases

- Potential candidates for BCT after neoadjuvant chemotherapy:
  - Unifocal disease
  - No inflammatory skin involvement
  - Radiographic abnormalities resectable with lumpectomy
  - No contraindication to adjuvant radiotherapy
  - Willing to accept slightly higher risk of local recurrence in conversion from mastectomy to BCT
- SLNB has been investigated both before and after the completion of neoadjuvant chemotherapy [69]. When performed before neoadjuvant chemotherapy, it is both accurate (identification rate between 93 and 100 %) and safe, with a low rate of regional recurrence reported. However, it potentially delays the initiation of chemotherapy in an era where lymph node status does not influence the choice of chemotherapy. Conversely, SLN biopsy after neoadjuvant chemotherapy has the advantage of reducing the number of operative procedures needed, as well as being both accurate and safe [69]. A 2011 meta-analysis examining the accuracy rate of SLNB after neoadjuvant chemotherapy reported that the detection rate was 82 to 100 %, with a false-negative rate of 0 to 20 % [70]. However, the data with regard to the axillary recurrence in this setting are limited [69]. Furthermore, the ACOSG Z01071 (Alliance) Trial demonstrated a false-negative rate of greater than 10 % in women with cN1 breast cancer and 2 or more sentinel lymph nodes examined following neoadjuvant chemotherapy [71]. The Canadian SN FNAC study showed a suboptimal identification rate of SLN after chemotherapy, but has shown an acceptable false-negative rate of 8.4 % when immunohistochemistry (IHC) is used and sentinel node metastases of any size are considered positive. After neoadjuvant therapy, accuracy is further increased by the use of both blue dye and radiolabelled tracer, as well as by harvesting more than one sentinel node if possible [72]. The clinical relevance of residual nodal disease in the axilla following neoadjuvant treatment remains undetermined. As a result, in patients who are node positive on presentation, axillary lymph node dissection is the standard of care following neoadjuvant chemotherapy, although there is a role for tailoring this to our individual patients with input from an MCC [69, 70].

Neoadjuvant chemotherapy studies

Study	Methods	Results
NSAPB B18 Wolmark et al. [68]	• *N* = 1493 • RCT • Operable T1–3 N0–1 M0 patients assigned to pre-operative chemo (4 cycles of AC) vs. post-operative chemo (4 cycles of AC)	• Follow-up—9 years • No differences in OS (70 % and 69 %) or DFS (53 % and 55 %) • Marginally statistically significant treatment by age interactions appears to be emerging for survival and DFS, suggesting that younger patients may benefit from preoperative therapy, whereas the reverse may be true for older patients

(continued)

(continued)

Study	Methods	Results
EORTC Trial 10902 van der Hage et al. [67]	• *N* = 698 • RCT • Patients with T1c, T2, T3, T4b, N0 to 1 and M0 breast cancer were assigned to pre-operative vs. post-operative chemotherapy (4 cycles—FEC)	• Median follow-up—56 months • No differences in terms of PFS, OS and LRR • Pre-operative chemotherapy enabled more patients to be treated with breast-conserving surgery (rate of downstaging was 23 %)
Fisher et al. 2011 [73]	• *N* = 385 • Retrospective chart review • Patients stage I, II or III and triple-negative treated with neoadjuvant or adjuvant chemotherapy	• There is a trend towards survival benefit in patients with pCR following neoadjuvant chemotherapy • However, patients undergoing neoadjuvant chemotherapy with residual disease had significantly worse survival compared to patients receiving adjuvant therapy, with a trend towards worse survival compared to patients receiving neoadjuvant chemotherapy with pCR

AC doxorubicin/adriamycin + cyclophosphomide, *RCT* randomised controlled trial, *DFS* disease-free survival, *FEC* fluorouracil, epirubicin and cyclophosphamide, *OS* overall survival, *PFS* progression-free survival, *LRR* locoregional recurrence, *pCR* complete pathologic response

Inflammatory Breast Cancer

Inflammatory breast cancer (IBC) is a rare clinicopathological entity characterised by rapid progression and aggressive behaviour which, as originally described, presents with erythema and edema with exaggerated hair-follicle pits, causing a peau d'orange appearance of the skin [75]. The rapid progression, along with diffuse erythema of more than one-third of the skin overlying the breast, distinguishes IBC from neglected LABC with skin involvement [75].

After ruling out metastasis, patients are usually treated with pre-operative chemotherapy followed by surgery and radiation [75, 76]. The combined approach improves the outcome of those patients with IBC. In a recent study, Li et al. reported a 5-year survival rate of 35–40 % [75].

Pregnancy and Breast Cancer

Pregnancy-associated breast cancer (PABC) is defined as breast cancer diagnosed during pregnancy, within 1 year of delivery, or while lactating [77]. It is considered one of the most common cancers diagnosed during pregnancy, with an incidence of 1 in 3000 pregnancies [78] and is usually of high grade. The management of PABC requires a multimodality approach and thorough discussion with the patient. Treatment depends on the stage of the cancer and the gestational age of the pregnancy.

Work-up	Before week 20	After week 20
• Mammogram (with fetal protection) • Breast ultrasound • Discuss at MCC	• Breast surgery is safe throughout the pregnancy: – Mastectomy and SLNB/axillary dissection – BCT: not common – Radiation can be delayed until after delivery. A typical patient undergoing BCT will have a lumpectomy performed followed by chemotherapy (see below) and RT after delivery – SLNB with technetium and excluding blue dye • Chemotherapy can be administered after the first trimester: – If the patient is planned for neoadjuvant chemotherapy, then breast conservation is possible	• If there is no contraindication to BCT, it can be preformed, with plans for post-partum radiation • SLNB with radiolabelled sulfur colloid and excluding blue dye

BCT breast-conserving therapy, *SLNB* sentinel lymph node biopsy, *RT* radiotherapy

Special Notes

- Fluorouracil, doxorubicin and cyclophosphamide can be used during the second and third trimesters of pregnancy; no complications were observed for the foetus or infant [79].
- NCCN guidelines suggest that insufficient evidence exists regarding the general use of taxanes in any trimester; however, the use of weekly paclitaxel after the first trimester may be acceptable if clinically indicated [80].
- The use of trastuzumab is contraindicated in all trimesters [80].
- Data would suggest that SLNB is safe in the pregnant population using Tc-99 m for lymphoscintigraphy [81, 80] but avoiding blue dye [83].
- MRI cannot be performed due to inability to administer gadolinium.

Metastatic Breast Cancer

Approximately 4.1 % of newly diagnosed breast cancer patients will have metastases at presentation. Improved systemic therapy has seen an increase in the 5-year survival of such patients in the past 5 years [84].

Until recently, surgery had a limited role in the management of patients with metastasis [85, 86]. However, there is an emerging body of evidence to support the concept that removing the primary may provide a survival advantage for such patients [84–86]. A retrospective review of 16,023 patients from the national cancer data base examined this issue. Overall survival was improved in women who underwent surgical resection, with 3-year survival rates of 17 % for the no-surgery group, 28 % for the partial mastectomy group and 32 % for the mastectomy group [85]. Several other retrospective studies showed survival benefits for surgery [87–95].

However, Cady et al. [96] challenged this view through a case-matched retrospective analysis of 808 patients with metastatic breast cancer. They found that case matching either diminishes or eliminates the survival advantage obtained with surgery. More recently, Badwe et al. demonstrated that locoregional treatment of the primary tumour and axillary nodes has no impact on overall survival in patients with metastatic disease at presentation who have responded to frontline chemotherapy [97]. Soran et al. drew a similar conclusion with respect to local therapy in metastatic disease, regardless of response to systemic treatment [98]. Additional trials are ongoing and should help to further clarify the issue [99, 100]. We believe that these cases constitute special situations that need a multidisciplinary approach. Each decision needs to be tailored according to patients' symptoms (pain, bleeding, non-healing wound), comorbidities and life expectancy. There are other ongoing phase III trials examining the value of early local therapy for the intact primary tumour in patients with metastatic breast cancer.

Locoregional Recurrence of Breast Cancer

Breast cancer recurrence can be divided into breast recurrence after breast-conserving therapy, recurrence after mastectomy and axillary recurrences [99].

Breast recurrence after BCT	Recurrence after mastectomy	Axillary recurrence
• Rate of LR after BCT—0.5–1 % per year [102] • Risk factors: – Age <45 years – High grade – Extensive DCIS – Node positive – HER2/neu overexpression – Positive margins • Most recurrences occur in the same quadrant as the primary tumour • Usually detected by physical examination and/or mammography • Metastatic work-up is required to rule out systemic disease • Due to previous radiotherapy, mastectomy is the standard of care, although data is beginning to emerge examining possible repeat excision and radiotherapy [31]	• Rate of chest wall recurrence: 5–7 % • The main predicting factor of chest wall recurrence is the stage of the initial tumour • Usually the recurrence after mastectomy carries a worse outcome than that after BCT • Metastatic work-up is indicated • If systemic disease is ruled out, the local treatment involves wide local excision with or without radiotherapy	• Rule out distant metastases and then patients treated with surgical excision of gross disease have better regional control than those treated by radiation therapy [103] • Isolated axillary recurrence has a 5-year survival of 50 % [104] • There is limited data on repeat irradiation of an already irradiated axilla and it should be discussed in the setting of a multidisciplinary meeting

BCT breast-conserving therapy, *LR* local recurrence

Referral to Medical Oncology

1. All invasive breast cancers need to be evaluated by medical oncology or discussed in MCC for consideration of systemic therapy.

Referral to Radiation Oncology

1. In situ or invasive carcinoma treated with breast-conserving therapy.
2. Positive or very close margins after mastectomy.
3. Any tumour more than 5 cm irrespective of the surgical treatment offered.
4. Locally advanced and inflammatory breast cancer.
5. Node-positive breast cancer.

Referring to Multidisciplinary Cancer Conference

Ideally all patients where time allows; however the following should be discussed:

1. Any case in which a deviation from the standard of care is considered.
2. Axillary lymph node metastases.
3. To review imaging and assess the extent of the disease for the purpose of planning surgical therapy.
4. Disease progression on neoadjuvant chemotherapy with borderline operability.
5. Patient with metastasis to contralateral axilla.
6. Patient with axillary metastasis and unknown primary cancer.
7. Chest wall recurrence after breast reconstruction.
8. Metastatic breast cancer in which surgery is being considered.

Breast Reconstruction

Over the last decade, there has been an increase in post-mastectomy breast reconstruction rates [105]. Research has shown that immediate and delayed breast reconstruction following mastectomy can improve patients' quality of life [104, 105] and is both technically and oncologically successful in the appropriate patients [108, 109]. Due to these advantages, we discuss and offer breast reconstruction as part of our initial management consultation. If a patient expresses interest in this option, a referral to plastic surgery is made.

Important considerations for reconstruction can be divided into pre-op, intra-op and post-operative concerns.

Pre-operative Considerations

Post-mastectomy reconstruction can be divided into implant-based and autologous methods. Implant-based reconstruction includes both direct to implant and tissue expander to implant procedures. Autologous methods include deep inferior epigastric perforator (DIEP) flaps, free and pedicled transverse rectus abdominis myocutaneous (TRAM) flaps, latissimus dorsi flaps and less commonly superficial inferior epigastric artery flaps (SIEA).

Post-mastectomy reconstruction can be done immediately (i.e. at the time of mastectomy) or in a delayed fashion. Delayed reconstruction is typically done at least 6 months following completion of any adjuvant treatment, but can technically be performed at any interval if the patient remains healthy and a good reconstruction candidate.

Mastectomy in the setting of immediate reconstruction can be done with a skin- or nipple-sparing technique. There are important oncologic factors to consider in such cases:

- A meta-analysis of >3700 patients demonstrated that skin-sparing mastectomy (SSM) with immediate reconstruction is equivalent to conventional mastectomy without reconstruction with respect to local and distant recurrence [110].
- Nipple-sparing mastectomy (NSM) can achieve good cosmetic results without an increased risk of recurrence in patients with disease >2 cm from the nipple [111]; however there are currently no randomised control trials on the oncologic safety of NSM vs. SSM. Similarly, there is minimal data on the oncologic safety of NSM in BRCA mutation carriers [112]. Overall, NSM should be carefully considered on a case-by-case basis in a multidisciplinary setting.

There are many clinical factors to consider when deciding on timing and type of reconstruction [113]. Immediate reconstruction is generally not recommended in:

- T3–T4 tumours
- Inflammatory breast cancer
- Axillary nodal metastases
- Before adjuvant radiotherapy
- When waiting for immediate reconstruction will considerably delay therapeutic surgery

Delayed breast reconstruction is acceptable in most circumstances.

Important patient factors that may adversely affect reconstruction outcomes include:

- Obesity
- Diabetes
- Smoking
- Older age

Intra-operative Considerations

Technically, SSM and NSM are more challenging than conventional mastectomy.

- Pectoralis coverage of the expander or implant is important. Therefore, when dissecting the breast and pectoralis fascia off the chest wall, it is imperative to avoid damaging the pectoralis major and compromising the muscle.
- Serratus fascia is used to form the inferior portion of the pocket for the expander or implant. This fascia must be kept intact. Occasionally this is augmented with an acellular dermal matrix.
- Excessive trauma to the mastectomy flaps must be avoided. Flaps must be thin enough to remove all breast tissue and constitute a sound oncologic procedure without compromising their viability.
- SLN biopsy at the time of SSM may be done through a separate incision in the conventional location, or via the SSM incision if nodes are easily accessible. Consider the need for excessive traction on the skin flap when making this decision. NSM requires a separate incision for SLN access as the NSM incision is often in the inframammary fold.
- ALND requires a separate incision in both SSM and NSM.

Post-operative Considerations

Complications [111]:

Autologous reconstruction	Implant-based reconstruction
Flap necrosis	Flap necrosis
Infection	Infection
Seroma	Seroma
Hematoma	Hematoma
Chronic back pain	Chronic breast pain
Abdominal weakness, bugle or hernia	Implant malposition
	Capsular contracture
TRAM flaps have a higher rate of donor site morbidity than DIEP flaps; conversely, DIEP flaps have a higher risk of necrosis [114–116]	Implant rupture

Surveillance [113, 117].

Surveillance is completed clinically. There is no evidence to support radiographic screening of the reconstructed breast unless the patient has palpable findings suggestive of recurrence. Suspicious masses or symptoms should be imaged and completely worked up. Fat necrosis is relatively common and benign following breast reconstruction.

Toronto Pearls

- When localising a lesion for breast conservation, some radiologists will mark the site of the lesion on the skin, but this is not always true. It is helpful to remember that the point of entry and the nipple are the only fixed points. The cranial-caudal (CC) view of a pre-operative mammogram defines medial vs. lateral and lesion along the nipples line will be either 12 or 6 o'clock. The medial-lateral (ML) view defines upper vs. lower half and lesions located at the nipple line will be located at either 3 or 9 o'clock.
- Z0011 results are integrated into our surgical practice: patients who have undergone lumpectomy and SLNB with positive nodes and who meet Z0011 criteria are not routinely offered completion axillary dissection.
- In cases of locally advanced breast cancer, we perform the SLNB after the neoadjuvant chemotherapy if nodes were clinically and radiologically negative prior to treatment. FNA of any suspicious axillary nodes is attempted pre-treatment. If nodes were positive, we recommend axillary lymph node dissection.
- Oncoplastic procedures in breast conservation are considered in conjunction with plastic surgery on a case-by-case basis, as are contralateral balancing procedures such as reduction mammoplasty.
- Contralateral prophylactic mastectomy (CPM) is not routinely recommended in the absence of a genetic mutation resulting in increased lifetime risk of developing a new breast cancer. In discussing CPM for patients without a gene mutation, the following must be considered: CPM does not offer an overall survival benefit in comparison to clinical and radiographic surveillance. It does decrease the risk of developing a contralateral breast cancer. CPM has no effect on local recurrence of the ipsilateral cancer. CPM may be considered in non-gene mutation carriers who are unable/unwilling to undergo continued surveillance and in those who wish to have immediate autologous flap-based reconstruction for optimal symmetry.

References

1. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian cancer statistics 2014. Toronto, ON: Canadian Cancer Society; 2014.
2. American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York, NY: Springer; 2010.
3. Hartmann LC, Sellers TA, Frost MH, et al. Benign breast disease and the risk of breast cancer. N Engl J Med. 2005;353:229–37.
4. Collins LC, Baer HJ, Tamimi RM, et al. Magnitude and laterality of breast cancer risk according to histologic type of atypical hyperplasia: results from the Nurses' Health Study. Cancer. 2007;109:180–7.
5. Fisher ER, Land SR, Fisher B, et al. Pathologic findings from the National Surgical Adjuvant Breast and Bowel Project: twelve-year observations concerning lobular carcinoma in situ. Cancer. 2004;100:238–44.
6. Masannat YA, Bains SK, Pinder SE, et al. Challenges in the management of pleomorphic lobular carcinoma in situ of the breast. Breast. 2013;22(2):194–6.

7. Sydnor MK, Wilson JD, Hijaz TA, et al. Underestimation of the presence of breast carcinoma in papillary lesions initially diagnosed at core-needle biopsy. Radiology. 2007;242:58–62.
8. Foley NM, Racz JM, Al-Hilli A, et al. An International Multicenter Review of the Malignancy Rate of Excised Papillomatous Breast Lesions. Ann Surg Oncol.
9. James BA, Cranor ML, Rosen PP. Carcinoma of the breast arising in microglandular adenosis. Am J Clin Pathol. 1993;100:507–13.
10. Koenig C, Dadmanesh F, Bratthauer GL, et al. Carcinoma arising in microglandular adenosis: an immunohistochemical analysis of 20 intraepithelial and invasive neoplasms. Int J Surg Pathol. 2000;8:303–15.
11. Brenner RJ, Jackman RJ, Parker SH, et al. Percutaneous core needle biopsy of radial scars of the breast: when is excision necessary? Am J Roentgenol. 2002;179:1179–84.
12. Peres A, Barranger E, Becette V, et al. Rates of upgrade to malignancy for 271 cases of flat epithelial atypia (FEA) diagnosed by breast core biopsy. Breast Cancer Res Treat. 2011.
13. Uzoaru I, Morgan BR, Liu ZG, et al. Flat epithelial atypia with and without atypical ductal hyperplasia: to re-excise or not. Results of a 5-year prospective study. Virchows Arch. 2012;461(4):419–23.
14. Becker AK, Gordon PB, Harrison DA, et al. Flat ductal intraepithelial neoplasia 1A diagnosed at stereotactic core needle biopsy: is excisional biopsy indicated? AJR Am J Roentgenol. 2013;200(3):682–8.
15. Eusebi V, Feudale E, Foschini MP, et al. Long-term follow-up of in situ carcinoma of the breast. Semin Diagn Pathol. 1994;11:223–35.
16. Virnig BA, Tuttle TM, Shamliyan T, et al. Ductal carcinoma in situ of the breast: a systematic review of incidence, treatment, and outcomes. J Natl Cancer Inst. 2010;102(3):170.
17. Collins LC, Tamimi RM, Baer HJ, et al. Outcome of patients with ductal carcinoma in situ untreated after diagnostic biopsy: results from the Nurses' Health Study. Cancer. 2005;103:1778–84.
18. Sanders ME, Schuyler PA, Dupont WD, et al. The natural history of low-grade ductal carcinoma in situ of the breast in women treated by biopsy only revealed over 30 years of long-term follow-up. Cancer. 2005;103:2481–4.
19. Fisher ER, Anderson S, Redmond C, et al. Pathologic findings from the national surgical adjuvant breast project protocol B-06. 10-year pathologic and clinical prognostic discriminants. Cancer. 1993;71:2507–14.
20. Boland GP, Chan KC, Knox WF, et al. Value of the Van Nuys prognostic index in prediction of recurrence of ductal carcinoma in situ after breast-conserving surgery. Br J Surg. 2003;90:426–32.
21. Fisher B, Dignam J, Wolmark N, et al. Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol. 1998;16(2):441–52.
22. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853--a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. J Clin Oncol. 2006;24(21):3381–7. Epub 2006 Jun 26.
23. Cuzick J, Sestak I, Pinder SE, et al. Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: long-term results from the UK/ANZ DCIS trial. Lancet Oncol. 2011;12:21–9.
24. Silverstein MJ. The University of Southern California/Van Nuys prognostic index for ductal carcinoma in situ of the breast. Am J Surg. 2003;186(4):337–43.
25. Hughes LL, Wang M, Page DL, et al. Local excision alone without irradiation for ductal carcinoma in situ of the breast: a trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2009;27(32):5319–24.
26. Wong JS, Chen YH, Gadd MA, et al. Eight-year update of a prospective study of wide excision alone for small low- or intermediate-grade ductal carcinoma in situ (DCIS). Breast Cancer Res Treat. 2014;143(2):343–50.
27. Fisher B, Dignam J, Wolmark N, et al. Tamoxifen in treatment of intraductal breast cancer: national surgical adjuvant breast and bowel project B-24 randomised controlled trial. Lancet. 1999;353:1993–2000.

28. Kell MR, Morrow M. An adequate margin of excision in ductal carcinoma in situ. BMJ. 2005;331:789–90.
29. Wang SY, Chu H, Shamliyan T, Jalal H, et al. Network meta-analysis of margin threshold for women with ductal carcinoma in situ. J Natl Cancer Inst. 2012;104(7):507–16.
30. Fisher B, Land S, Mamounas E, et al. Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the national surgical adjuvant breast and bowel project experience. Semin Oncol. 2001;28:400–18.
31. Resch A, Fellner C, Mock U, et al. Locally recurrent breast cancer: pulse dose rate brachytherapy for repeat irradiation following lumpectomy- a second chance to preserve the breast. Radiology. 2002;225:713–8.
32. Weaver DL, Ashikaga T, Krag DN, et al. Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med. 2011;364:412–21.
33. Baseline Staging Tests in Primary Breast Cancer. Hamm C, Tey R, reviewers Cancer care Ontario: Toronto (ON): Cancer Care Ontario; 2011. Available at: https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13868
34. Meric F, Mirza NQ, Vlastos G, et al. Positive surgical margins and ipsilateral breast tumor recurrence predict disease-specific survival after breast-conserving therapy. Cancer. 2003;97:926–33.
35. Hanley C, Kessaram R. Quality of diagnosis and surgical management of breast lesions in a community hospital: room for improvement? Can J Surg. 2006;49:185–92.
36. Warner E. Systematic review: using magnetic resonance imaging to screen for women at high risk for breast cancer. Ann Intern Med. 2008;148(9):671–9.
37. Sardanelli F, Boetes C, Borish B. Magnetic resonance imaging of the breast: recommendations from the EUSOMA working group. Eur J Cancer. 2010;46:1296–316.
38. Houssami N, Turner R, Morrow M. Preoperative magnetic resonance imaging in breast cancer: meta-analysis of surgical outcomes. Ann Surg. 2013;257(2):249–55.
39. Houssami N, Macaskill P, Marinovich ML. The association of surgical margins and local recurrence in women with early-stage invasive breast cancer treated with breast-conserving therapy: a meta-analysis. Ann Surg Oncol. 2014;21(3):717–30.
40. Moran MS, Schnitt SJ, Giuliano AE, et al. Society of surgical oncology-american society for radiation oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. Ann Surg Oncol. 2014;21(3):704–16.
41. Buchholz TA, Somerfield MR, Griggs JJ, et al. Margins for breast-conserving surgery with whole-breast irradiation in stage I and II invasive breast cancer: American Society of Clinical Oncology endorsement of the Society of Surgical Oncology/American Society for Radiation Oncology consensus guideline. J Clin Oncol. 2014;32(14):1502–6.
42. Steele RJ, Forrest AP, Gibson T, et al. The efficacy of lower axillary sampling in obtaining lymph node status in breast cancer: a controlled randomized trial. Br J Surg. 1985;72:368–9.
43. Krag D, Weaver D, Ashikaga T, et al. The sentinel node in breast cancer—a multicenter validation study. N Engl J Med. 1998;339:941–6.
44. Lyman GH, Giuliano AE, Somerfield MR, et al. American society of clinical oncology guideline recommendations for sentinel lymph node biopsy in early-stage breast cancer. J Clin Oncol. 2005;23:7703–20.
45. Mansel RE, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. J Natl Cancer Inst. 2006;98:599–609.
46. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
47. Fisher B, Montague E, Redmond C, et al. Findings from NSABP Protocol No. B-04-comparison of radical mastectomy with alternative treatments for primary breast cancer. I. Radiation compliance and its relation to treatment outcome. Cancer. 1980;46:1–13.

48. Galimberti V, Cole BF, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. Lancet Oncol. 2013;14(4):297–305.
49. Newman LA, Mamounas EP. Review of breast cancer clinical trials conducted by the National Surgical Adjuvant Breast Project. Surg Clin North Am. 2007;87:279–305. vii.
50. Giuliano AE, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. Ann Surg. 2010;252:426–32.
51. Orr RK. The impact of prophylactic axillary node dissection on breast cancer survival-a Bayesian meta-analysis. Ann Surg Oncol. 1999;6:109–16.
52. Joslyn SA. Hormone receptors in breast cancer: racial differences in distribution and survival. Breast Cancer Res Treat. 2002;73:45–59.
53. Truong PT, Bernstein V, Wai E, et al. Age-related variations in the use of axillary dissection: a survival analysis of 8038 women with T1-ST2 breast cancer. Int J Radiat Oncol Biol Phys. 2002;54:794–803.
54. Clarke M, Collins R, Darby S, et al. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet. 2005;366:2087–106.
55. Fisher B, Bauer M, Margolese R, et al. Five-year results of a randomized clinical trial comparing total mastectomy and segmental mastectomy with or without radiation in the treatment of breast cancer. N Engl J Med. 1985;312:665–73.
56. Cabanes PA, Salmon RJ, Vilcoq JR, et al. Value of axillary dissection in addition to lumpectomy and radiotherapy in early breast cancer. The Breast Carcinoma Collaborative Group of the Institut Curie. Lancet. 1992;339:1245–8.
57. Sanghani M, Balk EM, Cady B. Impact of axillary lymph node dissection on breast cancer outcome in clinically node negative patients: a systematic review and meta-analysis. Cancer. 2009;115:1613–20.
58. Donker M, van Tienhoven G, Straver ME, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981–22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial. Lancet Oncol. 2014;15:1303–10.
59. Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373:307–16.
60. Pilewskie ML, Morrow M. Management of the clinically node-negative axilla: what have we learned from the clinical trials? Oncology (Williston Park). 2014;28(5):371–8.
61. Dixon JJ. A companion to specialist surgical practice breast surgery. Philadelphia: Saunders Elsevier; 2009.
62. Chia S, Swain SM, Byrd DR, et al. Locally advanced and inflammatory breast cancer. J Clin Oncol. 2008;26:786–90.
63. Kaufmann M, von Minckwitz MG, Bear HD, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol. 2007;18:1927–34.
64. Colleoni M, Viale G, Zahrieh D, et al. Expression of ER, PgR, HER1, HER2, and response: a study of preoperative chemotherapy. Ann Oncol. 2008;19:465–72.
65. Rody A, Karn T, Solbach C, et al. The erbB2+ cluster of the intrinsic gene set predicts tumor response of breast cancer patients receiving neoadjuvant chemotherapy with docetaxel, doxorubicin and cyclophosphamide within the GEPARTRIO trial. Breast. 2007;16:235–40.
66. Braud AC, Asselain B, Scholl S, et al. Neoadjuvant chemotherapy in young breast cancer patients: correlation between response and relapse? Eur J Cancer. 1999;35:392–7.
67. van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol. 2001;19:4224–37.
68. Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr. 2001;96–102.

69. Sabel MS. Sentinel lymph node biopsy before or after neoadjuvant chemotherapy: pros and cons. Surg Oncol Clin N Am. 2010;19:519–38.
70. Tan VK, Goh BK, Fook-Chong S, et al. The feasibility and accuracy of sentinel lymph node biopsy in clinically node-negative patients after neoadjuvant chemotherapy for breast cancer—a systematic review and meta-analysis. J Surg Oncol. 2011;104:97–103.
71. Boughey JC, Suman VJ, Mittendorf EA, Ahrendt GM, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer. The ACOSOG Z1071 (Alliance) Clinical Trial. JAMA. 2013;310(14):1455–61.
72. Boileau JF, Poirier B, Basik M, Holloway C, et al. Sentinel node biopsy following neoadjuvant chemotherapy in biopsy proven node positive breast cancer: The SN FNAC study. J Clin Oncol. 2015;33(3):258–64.
73. Fisher CS, Ma CX, Gillanders WE, et al. Neoadjuvant chemotherapy is associated with improved survival compared with adjuvant chemotherapy in patients with triple-negative breast cancer only after complete pathologic response. Ann Surg Oncol. 2012;19:253–8.
74. Bell C. A system of operative surgery. Hale & Homer, 1814.
75. Li BD, Sicard MA, Ampil F, et al. Trimodal therapy for inflammatory breast cancer: a surgeon's perspective. Oncology. 2010;79:3–12.
76. Robertson FM, Bondy M, Yang W, et al. Inflammatory breast cancer: the disease, the biology, the treatment. CA Cancer J Clin. 2010;60:351–75.
77. Rosenkranz KM, Lucci A. Surgical treatment of pregnancy associated breast cancer. Breast Dis. 2005;23:87–93.
78. Amant F, Deckers S, Van CK, et al. Breast cancer in pregnancy: recommendations of an international consensus meeting. Eur J Cancer. 2010;46:3158–68.
79. Veronesi U, Zucali R, Luini A. Local control and survival in early breast cancer: the Milan trial. Int J Radiat Oncol Biol Phys. 1986;12:717–20.
80. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 3.2014. 04/01/2014. Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed 23 Oct 2014.
81. Mondi MM, Cuenca RE, Ollila DW, et al. Sentinel lymph node biopsy during pregnancy: initial clinical experience. Ann Surg Oncol. 2007;14:218–21.
82. Johnson MT, Guidroz JA, Smith BJ, et al. A single institutional experience of factors affecting successful identification of sentinel lymph node in breast cancer patients. Surgery. 2009;146:671–6.
83. Khera SY, Kiluk JV, Hasson DM, et al. Pregnancy-associated breast cancer patients can safely undergo lymphatic mapping. Breast J. 2008;14:250–4.
84. Pockaj BA, Wasif N, Dueck AC, et al. Metastasectomy and surgical resection of the primary tumor in patients with stage IV breast cancer: time for a second look? Ann Surg Oncol. 2010;17:2419–26.
85. Khan SA, Stewart AK, Morrow M. Does aggressive local therapy improve survival in metastatic breast cancer? Surgery. 2002;132:620–6.
86. Beslija S, Bonneterre J, Burstein HJ, et al. Third consensus on medical treatment of metastatic breast cancer. Ann Oncol. 2009;20:1771–85.
87. Fields RC, Jeffe DB, Trinkaus K, et al. Surgical resection of the primary tumor is associated with increased long-term survival in patients with stage IV breast cancer after controlling for site of metastasis. Ann Surg Oncol. 2007;14:3345–51.
88. Babiera GV, Rao R, Feng L, et al. Effect of primary tumor extirpation in breast cancer patients who present with stage IV disease and an intact primary tumor. Ann Surg Oncol. 2006;13:776–82.
89. Blanchard DK, Shetty PB, Hilsenbeck SG, et al. Association of surgery with improved survival in stage IV breast cancer patients. Ann Surg. 2008;247:732–8.
90. Neuman HB, Morrogh M, Gonen M, et al. Stage IV breast cancer in the era of targeted therapy: does surgery of the primary tumor matter? Cancer. 2010;116:1226–33.

91. Bafford AC, Burstein HJ, Barkley CR, et al. Breast surgery in stage IV breast cancer: impact of staging and patient selection on overall survival. Breast Cancer Res Treat. 2009;115:7–12.
92. Hazard HW, Gorla SR, Scholtens D, et al. Surgical resection of the primary tumor, chest wall control, and survival in women with metastatic breast cancer. Cancer. 2008;113:2011–9.
93. Ly BH, Vlastos G, Rapiti E, et al. Local-regional radiotherapy and surgery is associated with a significant survival advantage in metastatic breast cancer patients. Tumori. 2010;96:947–54.
94. Gnerlich J, Jeffe DB, Deshpande AD, et al. Surgical removal of the primary tumor increases overall survival in patients with metastatic breast cancer: analysis of the 1988-2003 SEER data. Ann Surg Oncol. 2007;14:2187–94.
95. Rao R, Feng L, Kuerer HM, et al. Timing of surgical intervention for the intact primary in stage IV breast cancer patients. Ann Surg Oncol. 2008;15:1696–702.
96. Cady B, Nathan NR, Michaelson JS, et al. Matched pair analyses of stage IV breast cancer with or without resection of primary breast site. Ann Surg Oncol. 2008;15:3384–95.
97. Badwe RA. A randomized trial to assess the impact of locoregional treatment on survival of patients with metastatic breast cancer at first presentation. Available from: http://clinicaltrials.gov/show/NCT00193778. Updated 2013. Presented at SABCS 2013. Accessed 27 Oct 2014.
98. Soran A. The effect of primary surgical treatment on survival in patients with metastatic breast cancer at diagnosis. http://clinicaltrials.gov/show/NCT00557986. Updated 2012. Presented at SABCS 2013. Accessed 27 Oct 2014.
99. Khan SA. A randomized phase III trial of the value of early local therapy for the intact primary tumor in patients with metastatic breast cancer. Available from: http://clinicaltrials.gov/show/NCT01242800. Updated 2014. Accessed 27 Oct 2014.
100. Piyapant A. Role of surgery for the primary in patients with breast cancer stage IV: a prospective randomized multicenter controlled trial. Available from: http://clinicaltrials.gov/show/NCT01906112. Updated 2014. Accessed 27 Oct 2014.
101. Easson AM, McCready DR. Management of local recurrence of breast cancer. Expert Rev Anticancer Ther. 2004;4:219–26.
102. Cabioglu N, Hunt KK, Buchholz TA, et al. Improving local control with breast-conserving therapy: a 27-year single-institution experience. Cancer. 2005;104:20–9.
103. Recht A, Pierce SM, Abner A, et al. Regional nodal failure after conservative surgery and radiotherapy for early-stage breast carcinoma. J Clin Oncol. 1991;9:988–96.
104. Willner J, Kiricuta IC, Kolbl O. Locoregional recurrence of breast cancer following mastectomy: always a fatal event? Results of univariate and multivariate analysis. Int J Radiat Oncol Biol Phys. 1997;37:853–63.
105. Albornoz CR, Bach PB, Mehrara BJ, et al. A paradigm shift in US breast reconstruction: increasing implant rates. Plast Reconstr Surg. 2013;131:15–23.
106. Stevens LS, McGrath MH, Druss RG, Gump FE, Forde KA. The psychological impact of immediate reconstruction for women with early breast cancer. Plast Reconstr Surg. 1984;73:619–28.
107. Schain WS. Breast Reconstruction. Update of psychosocial and pragmatic concerns. Cancer. 1991;68:1170–5.
108. Downes KJ, Glatt BS, Kanchwala SK, et al. Skin sparing mastectomy and immediate reconstruction is an acceptable treatment option for patients with high risk breast carcinoma. Cancer. 2005;103:906–13.
109. Chevray PM. Timing of Breast Reconstruction: Immediate versus Delayed. Cancer J. 2008;14(4):223–9.
110. Lantis S, Tekkis PP, Sgourakis G, et al. Comparison of skin-sparing mastectomy versus non-skin-sparing mastectomy for breast cancer: A meta-analysis of observational studies. Ann Surg. 2010;251:632–9.
111. Wijayanayagam A, Kumar AS, Rd F, et al. Optimaizing the total skin-sparing mastectomy. Arch Surg. 2008;143:38–45.
112. Yao K, Liederback E, Tang R, et al. Nipple-sparing mastectomy in BRCA ½ mutation carriers: An interim analysis and review of the literature. Ann Surg Oncol. 2015;22(2):370–6.

113. Shea-Budgell M, Quan ML, Mehling B, et al. Breasy reconstruction following prophylactic or therapeutic mastectomy for breast cancer: Recommendations from an evidence-based provincial guideline. Plast Surg. 2014;22(2):103–11.
114. Man LX, Selber JC, Serlettu JM. Abdominal wall following free TRAM or DIEP reconstruction: A meta-analysis and critical review. Plast Reconstr Surg. 2009;124:752–64.
115. Egeberg A, Rasmussen MK, Ahm SJ. Comparing the donor site morbidity using the DIEP, SIEA, or MS-TRAM flaps for breast reconstructive surgery : A meta-analysis. J Plast Reconstr Aesthet Surg. 2012;65:1474–80.
116. Futter CM, Weiler-Mithoff E, Hagen S, et al. Do pre-operative abdominal site exercises prevent post-operative donor site complications for women undergoing DIEP flap breast reconstruction? A two-centre, prospective randomised control trial. Br J Plast Surg. 2003;56:674–83.
117. Zakireh J, Fowble B, Esserman LJ. Application of screening principles to the reconstructed breast. J Clin Oncol. 2010;28:173–80.
118. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med. 2002;347:1233–41.
119. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med. 2002;347:1227–32.

Chapter 5
Cholangiocarcinoma

Koji Tomiyama, Sean Cleary, Carol-anne E. Moulton, and Paul F. Ridgway

Introduction

Cholangiocarcinoma is an uncommon cancer that occurs within the intrahepatic and extrahepatic portions of the bile duct system. In North America, the incidence of extrahepatic cholangiocarcinoma is 0.5–2 per 100,000 and 0.95 per 100,000 for intrahepatic cholangiocarcinoma [1]. Up to 50 % of patients will be lymph node (LN) positive at presentation, 5 % are multifocal tumors and 10–20 % will have peritoneal involvement at presentation. Risk factors for cholangiocarcinoma are: primary sclerosing cholangitis (PSC) with a lifetime risk 10–40 % [2, 3], parasitic infection [1], previous sphincteroplasty [4], congenital anomalies of the biliary tree (choledochal cyst, Caroli's disease, anomalous pancreaticobiliary duct junction) [5], and chronic biliary inflammatory disease (Hepatitis B/C, liver cirrhosis [6], recurrent pyogenic cholangitis). The most common presentation is painless jaundice and weight loss in the setting of extrahepatic duct involvement. In Western countries, 80 % are extrahepatic (20 % distal and 60 % hilar) and 20 % are intrahepatic.

K. Tomiyama, M.D., Ph.D.
Fellow, Hepatopancreatobiliary Surgery, University of Toronto, Toronto, ON, Canada
e-mail: kojitomy25@gmail.com

S. Cleary, M.D., M.Sc., M.P.H., F.R.C.S.C., F.A.C.S.
C.-a.E. Moulton, M.D., Ph.D., F.R.A.C.S. (✉)
Department of Surgery, University of Toronto, Toronto ON, Canada
e-mail: Sean.Cleary@uhn.ca; Carol-anne.Moulton@uhn.ca

P.F. Ridgway, M.D., M.Med.Sc., F.R.C.S.I.
Department of Surgery, Trinity College Dublin at Tallaght Hospital, Dublin, Ireland
e-mail: pridgway@rcsi.ie

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_5

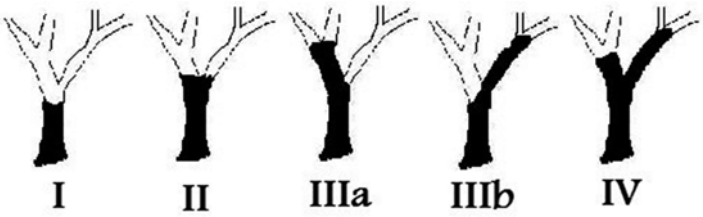
Presentation	Prognosis 5-year overall survival (OS)
• Distal extrahepatic localized, LN negative • Hilar extrahepatic localized, LN negative • Intrahepatic localized, LN negative	37–54 % (fully resected disease) 20–50 % (fully resected disease) 20–43 % (fully resected disease)
• LN postive—resectable	20–25 % [7] (median survival 22 months with positive margins, 60 months with negative margins) [8]
• Metastatic or unresectable disease	<5 %

LN lymph node

The recommended staging system is the Union for International Cancer Control and American Joint Committee on Cancer (UICC/AJCC) 7th edition. ICC and ECC are staged differently.

Definitions/Terminology

- **Extrahepatic Cholangiocarcinoma** (Bismuth/Corlett Classification system) [9]
  - Type 1: Distal to hepatic duct bifurcation **(Distal)**
  - Type 2: Involving the bifurcation **(Hilar)**
  - Type 3a/3b: Occlusion of common and either right (a) or left hepatic duct (b)
  - Type 4: Multicentric or involve bifurcation and both right and left hepatic ducts



Special Cases

Primary sclerosing cholangitis	Congenital cysts
• 6.8 % of patients develop cholangiocarcinoma over 10 years (10–40 % lifetime risk) • Incidence: 0.6 % per year • Usually presents within the first 2 years after diagnosis of PSC [10] • Screening recommendations: q6 month biliary imaging (CT or MRI/MRCP), Ca 19-9 for 2 years. However, no validated surveillance program in this population [1, 5] • There is some emerging evidence to support the use of EUS with biopsy/brushings in this scenario	• Incidence of cholangiocarcinoma <1 % per year • Overall life-time incidence of 28 %, if left untreated [11] • Upon identification, ductal imaging is necessary with MRCP; ERCP if needed • Recommend cyst excision with hepaticojejunostomy reconstruction • Cyst enterostomy is not recommended [12]

PSC primary sclerosing cholangitis, *ERCP* endoscopic retrograde cholangiopancreatography

Management

Intrahepatic Cholangiocarcinoma

Work-up	Management	Follow-up
• History and physical exam • Lab work: – Ca 19-9, AFP, CEA • Imaging: – CT chest, multiphasic CT A/P – MRI/MRCP • Search for primary adenocarcinoma of other site: – Endoscopy, chest CT, mammography [13]	• Surgical resection is the only potential cure • Removal of involved liver segments • There is emerging evidence that recommends a routine hilar LN dissection for its prognostic value [14] • M1 disease includes involvement of celiac, periaortic, caval LN	• CT C/A/P q3-6 mo × 2 years • However, there is no data to support that aggressive post operative surveillance as it has not been shown to alter outcome in this disease

LN lymph nodes, *CT C/A/P* Computed tomography of chest, abdomen, and pelvis

Special Notes

- Ca 19-9 can be elevated in up to 85 % of patients with cholangiocarcinoma, but is not specific; elevation can also occur in the setting of obstructive jaundice without malignancy. If it remains elevated after biliary decompression, it could indicate the presence of malignancy. Elevated pre- and post-operative Ca 19-9 predict poor survival [15].
- For perihilar tumors, decisions regarding which side of the liver to resect depend on right- or left-sided dominance, volume of future liver remnant, and the extent of vascular and ductal involvement.
- Some centers report that 30–50 % of tumors will be deemed unresectable at the time of surgery, despite accurate preoperative imaging [11].
- Quality Indicators: Pathologic Analysis—R0 margin, regional lymphadenectomy includes three or more LN.

Extrahepatic Cholangiocarcinoma

Site	Work-up	Management	Follow-up
Distal bile duct (below the cystic duct)	• History and physical exam • Labs: – Ca 19-9 • Imaging: – CT chest, multiphasic CT A/P – MRI/MRCP • Consider biliary decompression if: – Jaundice present with ERCP/PTC • Consider EUS for biopsy of lesion and lymph nodes (biopsy should be avoided in surgically resectable patients) [13] • Specificity of brush cytology is almost 100 %, but sensitivity only 18–40 % [16] • Consider serum IgG4 to rule out IgG4 related sclerosing cholangitis	• Surgical resection is the only potential cure • Pancreaticoduodenectomy including en-bloc resection of extrahepatic bile duct and gallbladder • Regional nodes include: – Hilar (CBD, common hepatic, portal, cystic) – Posterior and anterior pancreaticoduodenal – Nodes along SMV – Nodes along right lateral wall of SMA	• CT C/A/P q3-6 mo for 2 years • There is no data to support that aggressive surveillance alters outcome in this disease

(continued)

(continued)

Site	Work-up	Management	Follow-up
Hilar (above the cystic duct)		• En-bloc resection of extrahepatic bile duct and gallbladder, including right and left hepatectomy, or extended right/left hepatectomy [7] • Caudate lobe should be removed [13] • Regional nodes include: – Hilar (CBD, hepatic, portal, cystic) – Pericholedochal nodes in hepatoduodenal ligament	

ERCP endoscopic retrograde cholangiopancreatography, *PTC* percutaneous transhepatic cholangiography, *EUS* endoscopic ultrasound, *CBD* common bile duct, *SMV* superior mesenteric vein, *SMA* superior mesenteric artery

Special Notes

- In Ontario, all patients with known or suspected cholangiocarcinoma should be referred for management at a high-volume hepatopancreaticobiliary surgical oncology center.
- **Radiologic assessment** should include: level of involvement of the biliary tree, extent of vascular involvement, identification of hepatic lobar atrophy, and identification of metastatic disease [17].
- **Role of Frozen Section**: Although frozen section is frequently employed intraoperatively, it has differing uses depending on the type of cholangiocarcinoma. In extrahepatic cholangiocarcinoma, it has a definite mandatory role in determining margin status, unresectability or the presence of metastases. Frozen section margin status in intrahepatic cholangiocarcinoma is largely academic, as technical limitations dictate whether further margins are possible.
- **Role of Transplant in Hilar Cholangiocarcinoma:**
  - *Mayo Protocol* for patients with unresectable hilar cholangiocarcinoma or cholangiocarcinoma arising de novo in the setting of PSC is offered at UHN.
  - *Exclusion Criteria*—patients with intrahepatic cholangiocarcinoma, intrahepatic or extrahepatic metastases, gall bladder/below cystic duct involvement, tumor size ≥3 cm, Age ≥65 years old, Hx of malignancy within 5 years, Hx of prior RT in upper abdo, Prior hilar dissection within 12 months, any patients who underwent transperitoneal biopsy within 12 months.
  - ***Original Mayo protocol***; Preoperative Radiation—40–45 Gy, with concurrent 5-FU, followed by 20–30 Gy transcatheter irradiation with iridium. Capecitabine until transplantation.
  - ***UHN Mayo protocol***; Preoperative Radiation—Conformal RT boost, Local regional 45 Gy + Boost 54–75 Gy, with concurrent Capecitabine, Gemcitabine + Cisplatin until transplantation.

  - *Preoperative Assessment*—staging laparotomy (patients must be node negative, negative for metastases and no evidence of locally-advanced disease). Liberal endoscopic ultrasound and fine needle aspiration of regional nodes have identified occult metastatic disease prior to neoadjuvant therapy.
  - 5-year survival for patients who entered mayo protocol is 54 % and for patients transplanted is 73 % [18].
  - Fallout rate is about 30 % and median survival after fall out is 6.8 months [19].

- **Role of Medical Oncology**: There is no convincing data for the use of adjuvant therapy with "older" agents, based on subgroup analysis of larger heterogeneous trials. Many medical oncologists extrapolate the activity noted using the Gem-Cis regimen in the metastatic population [25] for use in adjuvant regimens, particularly for those with node positive disease.
- **Quality Indicators**: Margin: tumor margin of at least 5 mm or more [13]. Pathological analysis: regional lymphadenectomy includes 12 or more LN.

Unresectable/Metastatic Disease

Criteria of unresectability	Management
• Metastatic disease: – Liver, lung, peritoneum, distant lymph nodes (N2 disease: celiac, SMA nodes) • Patient factors: – Comorbidities rendering patient unable to tolerate potentially curative surgery • Anatomical factors: (adapted from Jarnagin et al. [20], JHPB surgery guidelines [23]) – Encasement of bilateral hepatic arteries or proper hepatic artery – Extension into secondary biliary radicals bilaterally with no chance for an R0 resection – Extension into biliary radicals unilaterally, with contralateral hepatic artery encasement/occlusion or contralateral atrophy of one hepatic lobe • Relative contraindication: – Atrophy of one hepatic lobe with contralateral portal vein encasement/occlusion—dependent upon the extent of portal vein involvement, this can be resected and reconstructed	• Consider transplant candidacy (Mayo protocol) if unresectable for local tumor invasion • Consider nonoperative approach to palliation if able (e.g., Stent/PTC placement) [21] and biopsy • Consider radiation/chemotherapy options

SMA superior mesenteric artery, *PTC* percutaneous transhepatic cholangiography/catheter

Landmark Publications

Prospective RCTs regarding surgical management of this disease are few, due to the relative rarity of the disease. Surgical management is largely dictated by consensus statements formed by large high volume centers.

Consensus guidelines	**ESMO clinical Practice guidelines: Biliary Cancer** Eckel et al. [22]		European guidelines
	Clinical Practice Guidelines: JSHBPS Kondo et al. [23]		Japanese guidelines
	AHPBA Summary statement: Hilar Cholangiocarcinoma Clary et al. [24]		North American guidelines
	SIGE/AIGO/AIOM/AIRO Position Paper Alvaro et al. [1]		Italian guidelines
	Study	**Methods**	**Results**
Medical oncology management	**UK-ABC-02** **Valle et al.** [25]	• RCT phase 3 • Conducted in 37 centers in the UK • *N*=410 patients • Non-resectable, recurrent, or metastatic biliary cancer (included intra/extrahepatic cholangiocarcinoma, ampullary, gallbladder cancer) • Two groups, Gemcitabine–Cisplatin or Gemcitabine alone for 24 weeks	• Median survival was 11.7 vs. 8.1 months for the Gemcitabine–Cisplatin and Gemcitabine-alone groups respectively (HR 0.64) • Significant improvement in progression free survival, 8 months vs. 5 months Gem-Cis vs. Gem respectively (HR 0.63) • The combination of Gem-Cis chemotherapy for advanced/metastatic disease gave an average of 3.6 months longer life than gemcitabine alone, with limited toxicity, and represents an appropriate option for treatment in these patients

RCT randomized controlled trial

Referring to Medical Oncology

1. R1 resection.
2. Presence of lymphovascular invasion/node positive disease.
3. Unresectable disease.

Referring to Radiation Oncology

1. R1 resection.
2. Palliative patients for consideration of symptomatic control/photodynamic therapy.
3. Locally advanced disease.

Referring to Multidisciplinary Cancer Conference (MCC)

1. R1 resection.
2. Locally advanced disease.
3. Unresectable disease.
4. All potentially resectable cases should be reviewed and treated at a high-volume HPB surgical oncology center.
5. Patients with PSC.
6. Mayo protocol candidate.

Toronto Pearls

- Strongly consider biliary decompression of future remnant liver for hilar tumor preoperatively and wait for near normal bilirubin levels if possible.
- Biliary decompression should occur prior to portal vein embolization (if required).
- Future remnant liver volume >40 % may be required.
- Caudate lobe resection should be considered in all cases, unless drainage of caudate duct into unaffected duct can be confirmed on MRCP and will not compromise surgical margin.
- Biliary infection/sepsis must be treated prior to proceeding to resection.
- Early and aggressive management of biliary infections in the postoperative period, considering drug resistant organisms if patient has had previous pre-op cholangitis and longer term antibiotic treatment AND never request a percutaneous biopsy in unresectable Klatskin's tumors if considering mayo protocol.

References

1. Alvaro D, Cannizzaro R, Labianca R, et al. Cholangiocarcinoma: a position paper by the Italian Society of Gastroenterology (SIGE), the Italian Association of Hospital Gastroenterology (AIGO), the Italian Association of Medical Oncology (AIOM) and the Italian Association of Oncological Radiotherapy (AIRO). Dig Liver Dis. 2010;42:831–8.

2. Burak K, Angulo P, Pasha TM, et al. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. Am J Gastroenterol. 2004;99:523–6.
3. Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. Gut. 1996;38:610–5.
4. Hakamada K, Sasaki M, Endoh M, et al. Late development of bile duct cancer after sphincteroplasty: a ten-to twenty-two year follow up study. Surgery. 1997;1215:488–92.
5. Roukounakis NE, Kuhn JA, McCarty TM. Association of an abnormal pancreaticobiliary junction with biliary tract cancers. Proc (Bayl Univ Med Cent). 2000;13:11–3.
6. Shaib YH, El-Serag HB, Davila JA, et al. Risk factors of intrahepatic cholangiocarcinoma in the United States: a case control study. Gastroenterology. 2005;128:620–6.
7. Alberts SR, Gores GJ, Kim GP, et al. Treatment options for hepatobiliary and pancreatic cancer. Mayo Clin Proc. 2007;82:628–37.
8. Burke EC, Jarnagin WR, Hochwald SN, et al. Hilar cholangiocarcinoma: patterns of spread, the importance of hepatic resection for curative operation, and a pre-surgical clinical staging system. Ann Surg. 1998;228:385–94.
9. Bismuth H, Corlette MB. Intrahepatic cholangioenteric anastomosis in carcinoma of the hilum of the liver. Surg Gynecol Obstet. 1975;140:170–8.
10. Bergquist A, Ekbom A, Olsson R, et al. Hepatic and extrahepatic malignancies in primary sclerosing cholangitis. J Hepatol. 2002;36:321–7.
11. Cleary SP, Knox J, Dawson L. Carcinoma of the biliary tract. In: Blanke CD, Rodel C, Talamonti MS, editors. Gastrointestinal oncology: a practical guide. Berlin: Springer; 2010. p. 251–99.
12. Stain SC, Guthrie CR, Yellin AE, Donovan AJ. Choledochal cyst in the adult. Ann Surg. 1995;222:128–33.
13. Khan SA, Davidson BR, Goldin R, et al. Guidelines for the diagnosis and treatment of cholangiocarcinoma: consensus document. Gut. 2002;51 Suppl 6:vi1–9.
14. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. J Hepatol. 2014;60:1268–89.
15. Kondo N, Murakami Y, Uemura K, et al. Elevated perioperative serum CA19-9 levels are independent predictors of poor survival in patients with resectable cholangiocarcinoma. J Surg Oncol. 2014;110:422–9.
16. Chapman R, Fevery J, Kalloo A, et al. Diagnosis and management of primary sclerosing cholangitis. Hepatology. 2010;51:660–78.
17. Cleary SP, Dawson LA, Knox JJ, Gallinger S. Cancer of the gallbladder and extrahepatic bile ducts. Curr Probl Surg. 2007;44:396–482.
18. Rosen CB, Heimbach JK, Gores GJ. Liver transplantation for cholangiocarcinoma. Transpl Int. 2010;23:692–7.
19. Sio TT, Martenson JA, Haddock MG, et al. Outcome of transplant-fallout patients with unresectable cholangiocarcinoma. Am J Clin Oncol. 2014;Jun 11. [Epub ahead of print].
20. Jarnagin WR, Fong Y, DeMatteo RP, et al. Staging, resectability, and outcome in 225 patients with hilar cholangiocarcinoma. Ann Surg. 2001;234:507–17.
21. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Engl J Med. 2001;344:1681–7.
22. Eckel F, Brunner T, Jelic S. On behalf of the ESMO Guidelines Working Group Biliary cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21 Suppl 5:v65–9.
23. Kondo S, Takada T, Miyazaki M, et al. Guidelines for the management of biliary tract and ampullary carcinomas: surgical treatment. J Hepatobiliary Pancreat Surg. 2008;15:41–54.
24. Clary B, Jarnigan W, Pitt H, et al. Hilar cholangiocarcinoma. J Gastrointest Surg. 2004;8: 298–302.
25. Valle J, Wasan H, Palmer D, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362:1273–81.

Chapter 6
Colon Cancer

Usmaan Hameed, Nancy Baxter, Zane Cohen, Robert Gryfe, Robin McLeod, and Fayez A. Quereshy

Introduction

Colorectal cancer is the third most common cancer in Canada, with an estimated 24,400 people diagnosed in 2014. Incidence is estimated at 59 per 100,000 in men, and 40 per 100,000 in women. It is the second leading cause of death from cancer in Canada [1]. The Canadian incidence of colon cancer in 2010 was approximately 14,000, which was double that of rectal cancer. Colon cancer accounts for the majority of deaths from colorectal cancer, with 6523 deaths in Canada compared to 1729 deaths due to rectal cancer in 2006. The 5-year relative survival for patients from 2004 to 2006 was 63 % [1]. Approximately 95 % of new cases and deaths occur in patients over the age of 50. The mortality from colorectal cancer has been in decline since 2004 for men and since 2000 for women, likely due to advances in systemic treatment and earlier detection due to screening efforts.

Presentation	Incidence [2] (%)	5-year survival [1] (%)
Localized Colorectal Cancer (Stage I, II)	49.5	90
Regional Colorectal Cancer (Stage III)	27.5	69
Metastatic Colorectal Cancer (Stage IV)	23.0	12

U. Hameed, M.D., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Usmaan.Hameed@nygh.on.ca

N. Baxter, M.D., Ph.D., F.R.C.S.C., F.A.C.S. • Z. Cohen, M.D., F.R.C.S.C., F.A.C.S.
R. Gryfe, M.D., Ph.D., F.R.C.S.C. • R. McLeod, M.D., F.R.C.S.C., F.A.C.S.
F.A. Quereshy, M.D., M.B.A., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: baxtern@smh.ca; zcohen@mtsinai.on.ca; rgryfe@mtsinai.on.ca;
robin.mcleod@cancercare.on.ca; fayez.quereshy@uhn.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_6

The current recommended staging system is the American Joint Committee on Cancer (AJCC) 7th edition.

Screening, Surveillance and High Risk Patients

Screening

Patient population	Recommendation
• Average risk: – Age > 50, asymptomatic, no family history	• FOBT or FIT beginning at age 50 with colonoscopy if positive • Repeat FOBT q2 years with • Flexible sigmoidoscopy q5 years • Colonoscopy also reasonable as initial test with repeat q10 years if normal
• Increased risk: – First degree relative with CRC < age 60	• Colonoscopy at age 50 or 10 years earlier than youngest affected relative • If negative, repeat q5 years or sooner depending on family history

FOBT fecal occult blood test, *FIT* fecal immunochemical test

Special Notes

- There is good quality evidence that population screening using either FOBT or flexible sigmoidoscopy has been shown to reduce colorectal cancer mortality [3, 4].
- FOBT has been shown to reduce relative risk of colorectal cancer mortality by 16 % [3, 4].
- A recent randomized trial from Norway showed that population screening with flexible sigmoidoscopy decreased colorectal cancer mortality (11.7/100,000 deaths per person-years absolute risk reduction) [5].
- A recent systematic review and meta-analysis showed decreased mortality for proximal cancers with colonoscopy compared to flexible sigmoidoscopy based on observational data [6].
- At least four randomized controlled trials and ten observational studies which have shown that screening with flexible sigmoidoscopy reduces incidence and mortality in distal, but not proximal colorectal cancer [6].
- Colonoscopy is recommended by the American College of Gastroenterology for screening, although there are no randomized trials demonstrating a reduction in mortality [7].
- A population-based study in Ontario of 2,412,077 people demonstrated that the colonoscopy rate was inversely proportional to death from colorectal cancer [8]. A case–control study in Ontario has demonstrated a significant association between colonoscopy and fewer deaths from colorectal cancer; specifically left sided cancers [9].

- Colonoscopy is the most sensitive of available screening options at detecting cancer or polyps and is thus an acceptable modality; however, it is associated with the highest risk and cost.
- A shorter interval between testing or repeat colonoscopy should be performed if the first colonoscopy is sub-optimal.
- Quality indicators for Colonoscopy:
  - Cecal intubation rate >90 %, adequate bowel preparation, post polypectomy bleeding rate of <0.5 % and perforation rate of <0.1 % [10, 11].
  - Polypectomy and adenoma detection rates are also important quality indicators; however there is no consensus on what the appropriate targets should be [10, 11].
  - There is insufficient evidence to suggest a minimum withdrawal time from the cecum of 6 min improves quality of endoscopy or improves the adenoma detection rate [10, 11].

Surveillance of Patients with Polyps Identified at Colonoscopy

Clinical scenario	Recommended surveillance interval (years)
• No polyps • <1 cm, hyperplastic polyps in sigmoid/rectum • <1 cm, 1–2 TA	10 10 5–10
• 3–10 TA • One or more TA ≥1 cm • Villous features or HGD	3
• More than ten adenomas	<3
Serrated lesions	
• SSA ≥1 cm • SSA with HGD • Traditional serrated adenoma	3
• Serrated polyposis syndrome	1

LGD low grade dysplasia, *TA* tubular adenoma, *HGD* high grade dysplasia, *SSA* sessile serrated adenoma

Adapted from: Guidelines for Colonoscopy Surveillance After Polypectomy: A Consensus Update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society [11]

Special Notes

- Patients with multiple colorectal adenomas (>10) should be considered for germline genetic testing of *APC*, *MUTYH*, and *MMR*.
- Above surveillance interval assumes (1) no family history of CRC in a first degree relative with an age of onset <60, (2) colonoscopy was complete and adequate, and all visible polyps were completely removed.

Hereditary Colorectal Cancer Syndromes

Colorectal cancer syndrome	Pattern of inheritance	Mutated germline gene	Colorectal cancer risk
Adenomatous			
Lynch syndrome (HNPCC)	AD	*MLH1, MSH2, MSH6, PMS2, EPCAM/TACSTD1*	40–80 % by age 75
Familial adenomatous polyposis (FAP)	AD	*APC*	90 % by age 45
Attenuated FAP (AFAP)	AD	*APC*	70 % by age 80
MUTYH-associated polyposis (MAP)	AR	*MUTYH*	35–55 %
Hamartomatous			
Peutz–Jeghers	AD	*STK1*	40 % by age 70
Juvenile polyposis	AD	*SMAD4, BMPR1A*	15–70 % by age 60

AD autosomal dominant, *AR* autosomal recessive

Microsatellite Instability and Lynch

Microsatellite instability (MSI) is identified in approximately 15 % of all colorectal cancers and is a feature of Lynch syndrome. The majority of cases of MSI are sporadic, due to methylation of an MMR gene, rather than a germline mutation found in Lynch. Lynch syndrome is transmitted in an autosomal dominant inheritance pattern and is the most common hereditary colorectal cancer syndrome, accounting for 2–3 % of all colorectal cancers. Revised Bethesda Guidelines provide criteria for testing to identify individuals at risk for Lynch [12]. Immunohistochemistry (IHC) testing for MMR.

Revised Bethesda Guidelines

- CRC diagnosed in a patient < age of 50
- Synchronous or metachronous CRC or other Lynch-related tumor
- CRC diagnosed in a first-degree relative with an Lynch-related tumor, one diagnosed < age 50
- CRC diagnosed in two or more first or second degree relatives with Lynch related tumors
- CRC with MSI-high histology in patient < 60 years of age:
  - Tumor infiltrating lymphocytes
  - Crohn's-like lymphocytic reaction
  - Medullary growth pattern
  - Mucinous/Signet ring differentiation

Special Notes

- In Stage II patients, IHC testing should be considered as high-frequency MSI has been shown to predict lack of benefit from fluorouracil-based adjuvant chemotherapy [13, 14]
- Extracolonic manifestations of Lynch include: cancers of the uterus (30–60 %), ovary (4–12 %), urinary tract (5–12 %), stomach (8–10 %), small bowel, pancreas (4 %), biliary tract, brain, and skin [15].
- Testing guidelines based on age and family history miss a significant proportion of patients with MSI-high tumors. Universal testing of patients with colorectal cancer is a more sensitive method of identifying MSI-high patients and may be more cost-effective than traditional guidelines [15–17].
- The proposed ASCO/ESMO guidelines suggest (1) universal testing of all patients with CRC or (2) testing of all patients <70 and patients >70 who fulfill any of the revised Bethesda guidelines [15]:
- Tumor testing for MMR deficiency with IHC ± MSI:
  - If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case.
  - If tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.
  - If loss of any of the other proteins (MSH2/MSH6/PMS2) identified, test for corresponding genes to the absent protein (e.g., MSH2, MSH6, EPCAM, PMS2, MLH1)
  - Full germline testing for Lynch should include DNA sequencing and large rearrangement analysis

Polyposis Syndromes

Familial Adenomatous Polyposis (FAP)

- >100–1000s of adenomas distributed in the colon and rectum at presentation.
- Accounts for <1 % of all CRC cancers. Polyps often manifest in adolescents or young adults.
- Extracolonic manifestations of FAP: gastric and duodenal polyps, desmoid tumors, thyroid and brain tumors, congenital hypertrophy of the retinal pigmented epithelium, supernumerary teeth, osteomas, and epidermoid cysts.
- Duodenal and ampullary adenocarcinomas follow CRC as the major cause of cancer death in patients with FAP

Attenuated Familial Adenomatous Polyposis (AFAP)

- 10–99 colorectal adenomas at presentation, preponderance for right colon. Polyps tend to develop later in life compared to FAP.

MUTYH-associated Polyposis (MAP)

- Autosomal recessive inheritance, phenotype characterized by <100 adenomas. Average age of onset mid-50s. Up to 1/3 of biallelic MUTYH-mutation carriers may develop CRC in the absence of colorectal polyposis.

Germline testing for APC and MUTYH [15]

- Should be considered in all patients with multiple colorectal adenomas (>10)
- APC germline testing should include DNA sequencing and large rearrangement analysis
- MUTYH germline testing
  - In white individuals: should begin with the most common mutations (G396D, Y179C) followed by analysis of the entire gene in heterozygotes.
  - In non-white individuals: full sequencing of MUTYH should be considered.

Management

Primary Localized Colon Cancer

Clinical scenario	Workup	Surgical management	Adjuvant therapy	Follow-up (FU)/surveillance
Malignant polyp	• History and physical exam • Colonoscopy with tattoo of site • Pathology review	• If incompletely resected or any high-risk features: resection with appropriate nodal basin • If resection required, laparoscopic approach recommended	• None	• Clinical assessment – Q3–6 months × 5 years • Colonoscopy at 1 year, then q5 years if normal

(continued)

(continued)

Clinical scenario	Workup	Surgical management	Adjuvant therapy	Follow-up (FU)/surveillance
Stage I, low risk Stage II	• History and physical exam • Labs: – CBC, CEA • Imaging: – CT chest/abdo/pelvis • Colonoscopy	• Resection with appropriate nodal basin • Laparoscopic resection recommended	• None	• Clinical assessment, CEA – Q3–6 months × 5 years • Colonoscopy at 1 year, then q5 years if normal • Stage II: annual CT chest/abdomen/pelvis [18–20]
High risk Stage II	• As above	• As above	• Consider 5-FU, capecitabine • Less benefit for MSI-high tumors [12, 13]	• As above
Stage III	• As above	• As above	• Recommend FOLFOX [21, 22] • Capecitabine may be given as alternative to 5-FU/LV [23]	• As above

Adapted from: Cancer Care Ontario Program in Evidence-Based Care: Follow-up Care, Surveillance Protocol, and Secondary Prevention Measures for Survivors of Colorectal Cancer 2012 [19]

Special Notes

- Polyps
  - High-risk features of malignant polyps include: poorly differentiated histology, lymphovascular invasion, tumor budding, and positive margin.
  - Management of sessile malignant polyps is controversial given estimates of a 10 % rate of lymph node involvement [24]. Patient age and comorbidities should be considered, as some patients may be better suited to observation.
- Adjuvant Treatment
  - High risk Stage II: perforation, obstruction, nodal harvest <12 nodes, T4, poorly differentiated histology. However, considering nodal harvest <12 nodes, young age, and obstruction as high risk is somewhat controversial.
  - Oxaliplatin is often omitted in Stage-II patients undergoing adjuvant chemotherapy due to adverse side-effects and unclear benefit

- Technical Considerations
  - Laparoscopic surgery is recommended in suitable patients in the absence of the following: locally advanced disease, obstruction, perforation, or fistula [25]. Evidence suggests that the principal benefit is reduction of hospital stay with equivalent oncological outcomes [24–29].
  - Quality Indicators:
    The resected specimen should contain a minimum of 12 lymph nodes [30, 31]
    A minimum 5 cm proximal and distal margin is preferred [30, 31]
- Surveillance
  - If a preoperative assessment was not performed, colonoscopy should be performed within 6 months of surgery or as soon as possible after the completion of adjuvant therapy. Frequency of colonoscopies thereafter should be dictated by the findings [11, 32, 33].
  - Eighty percent of patents recur within 2–2.5 years, and 95 % by 5 years.
  - Any new and persistent or worsening symptoms warrant the consideration of a recurrence.
  - The general practice at the University of Toronto is to perform CT of the chest/abdomen/pelvis at 6 months following completion of adjuvant therapy and then at 12 months and then annually.
  - There is evidence of a survival benefit with more intensive follow-up following surgery for colorectal cancer [32]. The American Society of Clinical Oncology (ASCO) 2013 endorsement of CCO practice guidelines suggests considering CT chest/abdomen every 6–12 months for 3 years in patients at a higher risk of recurrence [33].
  - The intensity of postoperative surveillance should depend on the likelihood that additional therapy would be recommended in the setting of recurrent disease.

Management of Patient Populations at High Risk for Colon Cancer

Clinical scenario	Screening	Surgical management	Surveillance
Lynch syndrome	• Colonoscopy q1–2 years beginning at age 20–25 or 10 years prior to youngest case in family	• Total colectomy at time of cancer diagnosis • Consider surgery also for HGD • Consider prophylactic TAH-BSO >35 years after childbearing is complete	• Endoscopic assessment of rectal stump q1–2 years • Gynecologic exam with transvaginal U/S and aspiration biopsy annually

(continued)

(continued)

Clinical scenario	Screening	Surgical management	Surveillance
FAP	• Flexible sigmoidoscopy (or colonoscopy) q1–2 years from age 10–12 • OGD with regular and side-viewing scope for duodenal adenomas from age 20–25 or when colonic polyposis diagnosed	• Surgery after development of large number of polyps or HGD: – Colectomy + IRA – TPC-IPAA – TPC with end ileostomy	• Colonoscopy q1–2 years for life in mutation carriers • Rectum present: endoscopic assessment q6-12 months • Ileal pouch: evaluation q1–3 years for pouch polyps • OGD interval depending on Spigelman stage
AFAP	• Colonoscopy (preponderance of right-sided adenomas) q1–2 years starting age 18–20 • OGD with regular and side-viewing scope for duodenal adenomas from age 20–25 or when colonic polyposis diagnosed	• As above for FAP • Extent of surgery depends on extent of polyposis and rectal involvement	• Surveillance interval depends on extent of polyposis • Colonoscopy q1–2 years in mutation carriers • Colonoscopy and polypectomy q1 year once adenomas are detected
MAP	• As above for FAP or AFAP, depending on extent of polyposis and family history	• As above for AFAP	• As above for AFAP
Ulcerative colitis/Crohn's colitis	• Colonoscopy q1–2 years beginning 8 years after diagnosis • Four quadrant biopsies every 10 cm	• Malignancy or dysplasia: TPC ± IPAA • Expert pathology review advisable	• Endoscopic assessment of rectal stump/ reservoir q 1–2 years

HNPCC hereditary non-polyposis coli syndrome, *FAP* familial adenomatous polyposis, *AFAP* attenuated FAP, *APC* adenomatous polyposis coli, *TAH-BSO* total abdominal hysterectomy + bilateral salpingo-oophorectomy, *TPC* total proctocolectomy, *IRA* ileorectal anastomosis, *IPAA* ileal pouch-anal anastomosis

Adapted from Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European society for medical oncology clinical practice guidelines [15]

Special Notes

- Lynch: Segmental resection may be considered in cases of significant comorbidity, advanced age, or locally advanced disease.
- FAP: The choice between Colectomy + IRA and TPC-IPAA must be balanced with patient age, degree of rectal polyposis, wish to bear children, risk of developing desmoids, and possibly the site of mutation in the APC gene.
- AFAP: Preservation of the rectum may be considered when rectal clearance is possible. The risk of recurrence in rectal stump must be balanced against the alteration in function with proctocolectomy and pelvic pouch.

Locally Advanced Colon Cancer or Locoregional Recurrence

Workup	Surgical management	Adjuvant therapy	Follow-up (F/U)
• History and physical exam • Labs: – CBC, CEA • Imaging: – CT chest/abdomen/pelvis – Consider MRI • Colonoscopy • Multidisciplinary review	• En-bloc resection with adjacent structures and negative margins • Consider neoadjuvant chemoradiotherapy to facilitate R0 resection (negative microscopic margins)	• Recommend FOLFOX; Capecitabine as alternative to 5-FU/LV • Adjuvant therapy for recurrence individualized based on previous regimen	• Clinical assessment at least q6 monthly for 3 years, then annually • Colonoscopy at 1 year, then q3–5 years • Consider CEA, imaging of liver/lungs

Special Notes

- Histologically negative margins should be the goal of en-bloc resection [34, 35]. Relevant margins should be marked on the specimen by the surgeon.

Colon Cancer with Distant Metastases

Workup	Surgery (referral to appropriate surgical sub-specialty)	Systemic management	Follow-up (F/U)
• History and physical exam • Labs: – CEA • Imaging: – CT chest/abdo/pelvis – Consider US or MRI liver as indicated – Consider US for ovarian metastases – CT head/bone scan for symptoms	• Liver: – Surgical resection with modern chemotherapy offers a 5-year OS up to 58 % • Lung: – Surgical resection with modern chemotherapy offers a 5-year OS up to 40 % • Peritoneum: – Referral to peritoneal malignancy program for evaluation • Ovary: – Bilateral oophorectomy should be considered if one ovary is involved • Brain: – Consider resection for solitary metastases	• FOLFOX or FOLFIRI with bevacizumab recommended [36–38] • Cetuximab can be considered for K-Ras wild type [39] • Consider a clinical trial	• Patients receiving chemotherapy with potentially resectable metastatic disease should have imaging every three cycles to assess response to therapy • CEA should be done only if patients do not have measurable disease on imaging • Patients in palliative care should only have blood tests and or imaging as dictated by clinical condition

Special Notes

- Resection of the primary tumor should be considered in symptomatic patients or in those with potentially resectable metastatic disease.
- First line chemotherapy should be strongly considered in asymptomatic patients with metastatic disease.
- Patients with unresected primaries should be followed as up to 20 % need surgical resection during the course of treatment
- There may be a survival advantage in resection of the primary tumor in patients with unresectable metastatic disease [40].

Landmark Publications

Topic	Study	Methods	Results
Laparoscopic vs. Open Resection	COST Trial [26] Fleshman et al., 2007 Update [41]	• RCT • *N* = 872 • Colon cancer only	• No significant difference in time to recurrence or OS, median F/U 7 years • Shorter median hospital stay
	CLASSIC Trial Jayne et al. [27]	• RCT • *N* = 794 (526 laparoscopic, 48 % rectal cancer)	• No difference in 3 year OS or LR
	COLOR Trial Buunen et al. [42]	• RCT • *N* = 1248 (excluded BMI >30) • Colon cancer only	• A 3 year difference in OS could not be ruled out in favor of open colectomy
	Barcelona Trial Lacy et al. [30] Lacy et al. [43] Update	• RCT • *N* = 219 • Colon cancer only	• Trend toward higher cancer-related survival in laparoscopic • Shorter hospital stay
Chemotherapy	NSABP C-07 Kuebler et al. [21]	• RCT • *N* = 2407 • Stage II/III resected with curative intent • 5-FU/LV alone (FUFA) vs. 5-FU/LV+ Oxaliplatin (FLOX)	• 4-year DFS (Stage II and III): – 73.2 % FLOX – 67 % FUFA
	MOSAIC Andre et al. [22] Andre et al., 2009 Update [44] Tournigand et al. [45] (sub-group analysis)	• RCT • *N* = 2246 • Stage II/III colon cancer resected with curative intent • FOLFOX4 vs. 5-FU/LV	• 5-year DFS (Stage II and III): – 73.3 % FOLFOX4 – 67.4 % 5-FU/LV • 6-year OS (Stage III): – 72.9 % FOLFOX4 – 68.7 % 5-FU/LV • Stage II: – No improvement in DFS/OS – No difference in DFS/OS in low vs. high-risk
	X-ACT Twelves et al. [18] Twelves et al., Update 2012 [46]	• RCT • *N* = 1987 • Capecitabine vs. Bolus 5-FU/LV in resected Stage III colon cancer	• Equivalent DFS and OS for capecitabine and 5-FU/LV, with few adverse events • Median follow-up 6.9 years

OS overall survival, *F/U* follow-up, *LR* local recurrence, *DFS* disease-free survival, *RCT* randomized controlled trial

Referring to Medical Oncology

1. High-risk Stage II.
2. Stage III, IV.
3. Locally advanced, Recurrent.

Referring to Radiation Oncology

1. Consider for T4b disease.

Referring to Multidisciplinary Cancer Conference (MCC)

1. Locally advanced or recurrent disease.
2. Metastatic disease in fit patients (synchronous and metachronous).

Toronto Pearls

- Neoadjuvant chemoradiotherapy for locally advanced or recurrent colon cancer may improve resectability and negative margin rates. Careful preoperative planning and multidisciplinary approach are necessary to achieve the goal of R0 resection [47].

References

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian cancer statistics 2014. Toronto, ON: Canadian Cancer Society; 2014.
2. Colorectal Cancer Staging and Survival. Toronto, ON: Canadian Partnership Against Cancer; 2010.
3. Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. Am J Gastroenterol. 2008;103(6):1541–9.
4. Holme O, Bretthauer M, Fretheim A, Odgaard-Jensen J, Hoff G. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. Cochrane Database of Syst Rev. 2013;9:CD009259.
5. Holme O, Loberg M, Kalager M, Bretthauer M, Hernan MA, Aas E, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA. 2014;312(6):606–15.
6. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ. 2014;348:g2467.

7. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol. 2009;104(3):739–50.
8. Rabeneck L, Paszat LF, Saskin R, Stukel TA. Association between colonoscopy rates and colorectal cancer mortality. Am J Gastroenterol. 2010;105(7):1627–32.
9. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009;150(1):1–8.
10. Tinmouth J, Kennedy EB, Baron D, Burke M, Feinberg S, Gould M, et al. Colonoscopy quality assurance in Ontario: systematic review and clinical practice guideline. Can J Gastroenterol Hepatol. 2014;28(5):251–74.
11. Lieberman DA, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR, et al. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2012;143(3):844–57.
12. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst. 2004;96(4):261–8.
13. Ribic CM, Sargent DJ, Moore MJ, et al. Tumor microsatellite-instability status as a predictor of benefit from fluorouracil-based adjuvant chemotherapy for colon cancer. N Engl J Med. 2003;349(3):247–57.
14. Sargent DJ, Marsoni S, Monges G, et al. Defective mismatch repair as a predictive marker for lack of efficacy of fluorouracil-based adjuvant therapy in colon cancer. J Clin Oncol. 2010;28(20):3219–26.
15. Stoffel EM, Mangu PB, Gruber SB, Hamilton SR, Kalady MF, Lau MW, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology clinical practice guideline endorsement of the familial risk-colorectal cancer: European society for medical oncology clinical practice guidelines. J Clin Oncol. 2015;33(2):209–17.
16. Matloff J, Lucas A, Polydorides AD, Itzkowitz SH. Molecular tumor testing for Lynch syndrome in patients with colorectal cancer. J Natl Compr Canc Netw. 2013;11(11):1380–5.
17. Perez-Carbonell L, Ruiz-Ponte C, Guarinos C, Alenda C, Paya A, Brea A, et al. Comparison between universal molecular screening for Lynch syndrome and revised Bethesda guidelines in a large population-based cohort of patients with colorectal cancer. Gut. 2012;61(6):865–72.
18. Jeffery M, Hickey BE, Hider PN. Follow-up strategies for patients treated for non-metastatic colorectal cancer. Cochrane Database Syst Rev. 2007;1:002200.
19. Figueredo A, Rumble RB, Maroun J, et al. The members of the Gastrointestinal Cancer Disease Site Group. Follow-up of patients with curatively resected colorectal cancer. Practice Guideline Report #2–9. June 16, 2010.
20. Earle C, Annis R, Sussman J, Haynes AE, Vafaei A. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer. Toronto, ON: Cancer Care Ontario; 2012. Program in Evidence-based Care Evidence-Based Series No.: 26-2.
21. Kuebler JP, Wieand HS, O'Connell MJ, et al. Oxaliplatin combined with weekly bolus fluorouracil and leucovorin as surgical adjuvant chemotherapy for stage II and III colon cancer: results from NSABP C-07. J Clin Oncol. 2007;25(16):2198–204.
22. Andre T, Boni C, Mounedji-Boudiaf L, et al. Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) Investigators. Oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment for colon cancer. N Engl J Med 2004;350(23):2343–51.
23. Twelves C, Wong A, Nowacki MP, et al. Capecitabine as adjuvant treatment for stage III colon cancer. N Engl J Med. 2005;352(26):2696–704.
24. Nivatvongs S, Rojanasakul A, Reiman HM, et al. The risk of lymph node metastasis in colorectal polyps with invasive adenocarcinoma. Dis Colon Rectum. 1991;34(4):323–8.
25. Smith A, Rumble RB, Langer B, et al. Laparoscopic surgery for cancer of the colon. Toronto, ON: Cancer Care Ontario; 2005. Program in Evidence-Based Care. Evidence-based Series #2-20-2.

26. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004;350(20):2050–9.
27. Jayne DG, Guillou PJ, Thorpe H, et al. Randomized trial of laparoscopic-assisted resection of colorectal carcinoma: 3-year results of the UK MRC CLASICC Trial Group. J Clin Oncol. 2007;25(21):3061–8.
28. Lacy AM, Garcia-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet. 2002;359(9325):2224–9.
29. Kuhry E, Schwenk W, Gaupset R, et al. Long-term outcome of laparoscopic surgery for colorectal cancer: a cochrane systematic review of randomised controlled trials. Cancer Treat Rev. 2008;34(6):498–504.
30. Le Voyer TE, Sigurdson ER, Hanlon AL, et al. Colon cancer survival is associated with increasing number of lymph nodes analyzed: a secondary survey of intergroup trial INT-0089. J Clin Oncol. 2003;21(15):2912–9.
31. Smith AJ, Driman DK, Spithoff K, et al. Guideline for optimization of colorectal cancer surgery and pathology. J Surg Oncol. 2010;101(1):5–12.
32. Tjandra JJ, Chan MK. Follow-up after curative resection of colorectal cancer: a meta-analysis. Dis Colon Rectum. 2007;50(11):1783–99.
33. Meyerhardt JA, Mangu PB, Flynn PJ, Korde L, Loprinzi CL, Minsky BD, et al. Follow-up care, surveillance protocol, and secondary prevention measures for survivors of colorectal cancer: American Society of Clinical Oncology clinical practice guideline endorsement. J Clin Oncol. 2013;31(35):4465–70.
34. Bowne WB, Lee B, Wong WD, et al. Operative salvage for locoregional recurrent colon cancer after curative resection: an analysis of 100 cases. Dis Colon Rectum. 2005;48(5):897–909.
35. Smith AJ, Driman DK, Spithoff K, McLeod R, Hunter A, Rumble RB, et al. Optimization of surgical and pathological quality performance in radical surgery for colon and rectal cancer: margins and lymph nodes. Toronto, ON: Cancer Care Ontario; 2008. [In review 2013 Dec]. Program in Evidence-based Care Evidence-based Series No.: 7-14 IN REVIEW.
36. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med. 2004;350(23):2335–42.
37. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol. 2007;25(12):1539–44.
38. Saltz LB, Clarke S, Diaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol. 2008;26:2013–9. Erratum appears in J Clin Oncol. 2009;27(4):653.
39. Van Cutsem E, Kohne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408–17.
40. Faron M, Pignon JP, Malka D, Bourredjem A, Douillard JY, Adenis A, et al. Is primary tumour resection associated with survival improvement in patients with colorectal cancer and unresectable synchronous metastases? A pooled analysis of individual data from four randomised trials. Eur J Cancer. 2015;51(2):166–76.
41. Fleshman J, Sargent DJ, Green E, et al. Laparoscopic colectomy for cancer is not inferior to open surgery based on 5-year data from the COST Study Group trial. Ann Surg. 2007;246(4):655–62. discussion 662–4.
42. Colon Cancer Laparoscopic or Open Resection Study Group, Buunen M, Veldkamp R, Hop WC, Kuhry E, Jeekel J, et al. Survival after laparoscopic surgery versus open surgery for colon cancer: long-term outcome of a randomised clinical trial. Lancet Oncol. 2009;10(1):44–52.
43. Lacy AM, Delgado S, Castells A, et al. The long-term results of a randomized clinical trial of laparoscopy-assisted versus open surgery for colon cancer. Ann Surg. 2008;248(1):1–7.

44. Andre T, Boni C, Navarro M, et al. Improved overall survival with oxaliplatin, fluorouracil, and leucovorin as adjuvant treatment in stage II or III colon cancer in the MOSAIC trial. J Clin Oncol. 2009;27(19):3109–16.
45. Tournigand C, Andre T, Bonnetain F, Chibaudel B, Lledo G, Hickish T, et al. Adjuvant therapy with fluorouracil and oxaliplatin in stage II and elderly patients (between ages 70 and 75 years) with colon cancer: subgroup analyses of the Multicenter International Study of Oxaliplatin, Fluorouracil, and Leucovorin in the Adjuvant Treatment of Colon Cancer trial. J Clin Oncol. 2012;30(27):3353–60.
46. Twelves C, Scheithauer W, McKendrick J, Seitz JF, Van Hazel G, Wong A, et al. Capecitabine versus 5-fluorouracil/folinic acid as adjuvant therapy for stage III colon cancer: final results from the X-ACT trial with analysis by age and preliminary evidence of a pharmacodynamic marker of efficacy. Ann Oncol. 2012;23(5):1190–7.
47. Cukier M, Smith AJ, Milot L, Chu W, Chung H, Fenech D, et al. Neoadjuvant chemoradiotherapy and multivisceral resection for primary locally advanced adherent colon cancer: a single institution experience. Eur J Surg Oncol. 2012;38(8):677–82.

Chapter 7
Colorectal Liver Metastases

Melanie E. Tsang, Shiva Jayaraman, Paul J. Karanicolas, and Alice C. Wei

Introduction

The liver is the most common site of metastases from colorectal cancer (CRC). Approximately 15 % of patients with CRC present with synchronous liver metastases, and 15 % of patients will develop metachronous metastases to the liver [1–3]. Of the patients who develop liver metastases, 80 % have unresectable disease at presentation [4]. Whether to resect the liver metastases depends on technical factors and prognostic variables.

	Prognosis [5–10]	
Presentation	5-year OS	10-year OS
• Resected CRLM	39–58 %	17–28 %
• Unresectable CRLM	5.3 %	NA

OS overall survival, *CRLM* colorectal liver metastases, *NA* not available

Commonly Used Prognostic Variables

Various clinical risk scores have been developed to help clinicians estimate survival outcomes for individual patients. They are valuable tools to assist clinicians in treatment decision-making.

M.E. Tsang, M.D., M.Sc., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: melanie.tsang@mail.utoronto.ca

S. Jayaraman, M.D., ME.Sc., F.R.C.S.C., F.A.C.S. • P.J. Karanicolas, M.D., Ph.D., F.R.C.S.C.
A.C. Wei, M.D., M.Sc., F.R.C.S.C., F.A.C.S.,
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: jayars@stjoe.on.ca; Paul.Karanicolas@sunnybrook.ca; alice.wei@uhn.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_7

Nordlinger et al. [11]	Variables	Score	2-year OS (%)
	• Age > 60 years • Size > 5 cm • Extension of primary into serosa • Lymphatic spread • Disease-free interval ≤ 2 years • ≥4 lesions • Resection margin < 1 cm	0–2 (low risk) 3–4 (intermediate risk) 5–7 (high risk)	79 60 43
Fong criteria Fong et al. [12]	Variables	Score	5-year OS (%)
	• Size > 5 cm • >1 lesion • CEA level > 200 ng/mL • Node positive primary • Disease-free interval < 12 months	0 1 2 3 4 5	60 44 40 20 25 14

OS overall survival, *CEA* carcinoembryonic antigen

Assessment of Resectability [13]

Oncologic criteria	Technical criteria
1. Prior to considering resection of CRC hepatic metastases, pretreatment radiological staging is required to assess for the presence and extent of intrahepatic and extrahepatic disease 2. Patients harboring limited EHD or with reasonable expectations for long-term control with adjuvant therapies may be considered for a hepatic resection 3. For patients with significant progression of metastatic disease during treatment with optimal preoperative chemotherapy, care should be individualized. Consider deferring surgical resection until disease control achieved with second-line systemic or regional therapies	1. Resectability includes the expectation that an R0 margin can be achieved 2. The technical feasibility of a hepatic resection should be based on four criteria related to the liver remnant after resection: (a) The anticipated ability to preserve two contiguous segments (b) The anticipated ability to preserve adequate vascular inflow, outflow and biliary drainage (c) The anticipated ability to preserve adequate FLR volume (20 % in normal liver and 30 % in pretreated liver with chemotherapy) (d) The demonstrated ability of the FLR to adequately function based on the appropriate regenerative response after PVE in patients with a marginal FLR volume and/or underlying liver disease

FLR future liver remnant, *EHD* extrahepatic disease

Special Notes

- Hold chemotherapy 3–4 weeks prior to liver resection.
- Hold bevacizumab for 6 weeks prior to liver resection to reduce the risk of bleeding.

- Laparoscopic resection in carefully selected patients in centers with expertise in minimally invasive surgery has been shown to be oncologically similar to open hepatectomy, with potential improvement in perioperative factors [14–16].

Management of CRLM

General Considerations

Work-up	Follow-up
Labs: • CEA level • LFTs **Imaging**: • CT chest, abdomen, pelvis • Consider MRI with liver-specific contrast agent (e.g., gadoexetic acid) if lesions are not well seen **Colonoscopy** within the preceding 18 months	Every 3–6 months for the first 2 years then every 6 months thereafter: CT chest, abdomen, pelvis CEA level Colonoscopy at 1 year

Surgical Considerations in Resectable Disease

Synchronous metastases (within 12 months of the diagnosis of the primary)

Strategy		Management
Simultaneous resection		1. Uncomplicated colon + liver resection (especially right-sided colonic resection) 2. Complicated colon resection + limited liver resection
Staged resection		1. Complicated rectal resection, extensive colon resection (especially left side) 2. Complicated liver resection (>4 segments)
	Primary first	Traditional approach **Advantage**: Avoids potential complications from primary disease (bleeding, perforation) **Disadvantage**: Postoperative complications can delay resection of hepatic disease which may progress to unresectability
	Liver resection first	Consider in • Extensive hepatic disease with asymptomatic primary • Patients with metastatic rectal cancer who must wait 8–12 weeks after chemoradiation before primary is resected **Advantages**: Early control of CRLM with opportunity to eradicate all hepatic disease. Complications from primary resection will not delay/prevent resection of metastatic disease **Disadvantages**: Primary may progress to unresectability or complications from progression may develop. Patient has had unnecessary liver resection, delaying palliative systemic treatment
Parenchyma preservation		Parenchymal sparing approach to resection may decrease morbidity and mortality Provides equivalent oncologic outcomes [17, 18]

Special Notes

- All cases of synchronous disease should be reviewed at MCC and considered for perioperative systemic treatment (see below)
- Sequence for staged resection is controversial and should be individualized [19]

Bilobar disease

Strategy	Management
One stage hepatectomy	If resectable with adequate liver volume, resect with one stage hepatectomy
Two stage hepatectomy	**First stage hepatectomy**: Wedge resections of the left lobe (clear the future liver remnant) **or** Segment 2, 3 resection **Right portal vein embolization**: Await 6 weeks to allow hypertrophy Continue chemotherapy after PVE until second stage hepatectomy **Second stage hepatectomy**: Resection of right lobe

Systemic Treatment

Role of perioperative chemotherapy

Strategy	Management	Advantage	Disadvantage
Upfront resection	Resect if resectable followed by post-liver resection chemotherapy	Avoids hepatotoxic therapy	May delay systemic treatment for micrometastatic disease
Perioperative chemotherapy	4–6 cycles of preoperative chemotherapy, followed by resection with post-liver resection chemotherapy	Could decrease extent of resection Increase rate of R0 resection Early treatment of micrometastatic disease Can assess tumor response to chemotherapy (e.g., improvement vs. progression of hepatic disease or development of extrahepatic disease) which may alter treatment trajectories	Could render hepatic disease invisible to imaging Hepatic toxicity of systemic treatments may affect surgical outcomes [20]

Conversion of unresectable liver metastases with chemotherapy

Strategy	Management	Follow-up
Conversion of unresectable hepatic disease	**After discussing in MCC**: Downstage with FOLFOX or FOLFIRI ± bevacizumab Consider cetuximab in patients with KRAS wild type tumors If becomes resectable, undertake resection Resection based on pre-downstaged lesions (i.e., resect the "ghosts" if possible). If not possible to safely resect the ghost lesions, follow closely and treat accordingly	Resume chemotherapy after surgery Close follow-up for return of "ghost" lesions

MCC multidisciplinary cancer conference

Extrahepatic Metastases (EHM) [6, 21–23]

Site of EHM	Management
Lung	Staged procedure only if both HPB and thoracic surgeons deem tumors resectable May be role to follow subcentimeter pulmonary nodules (SPN) Presence of SPN should not preclude hepatic resection Liver resection first, followed by lung resection Preoperative chemotherapy
Portal lymph nodes	Simultaneous procedure Survival at 5 years 12–33 % in recent series Individualized therapy based on assessment of tumor biology
Peritoneum	Should be assessed in conjunction with a peritoneal malignancy program
Ovary	Survival benefit in retrospective studies Resection should be considered if complete resection can be achieved
Retroperitoneal lymph nodes	Poor prognosis (5 year OS 0–7 %) Should be considered for clinical trial

MCC multidisciplinary cancer conference, *SPN* subcentimeter pulmonary nodule

Special Notes

- All cases of EHM should be reviewed at MCC and considered for perioperative systemic treatment

Liver-Directed Therapies

	Mechanism	Advantage	Disadvantage
Radiofrequency ablation (RFA)	Direct current transmission into tissue	Can be used for selected patients with otherwise unresectable disease (due to patient or disease factors) or to clear liver to extend resectability [24]	Unpredictable results as functions on impedance which changes during ablation Incomplete ablation with lesions >3 cm Cannot be used near large vessels or portal structures due to heat sink and potential damage to structures
Microwave ablation (MWA)	Microwave energy agitates water molecules to create heat	As above More uniform/predictable ablation zone than RFA [25]	Limit on size of treatable lesions

Evolving Techniques

	Technique	Advantage	Disadvantage
ALPPS (associating liver partition with portal vein ligation for staged hepatectomy) [26]	Staged hepatectomy In situ ligation of the right portal vein and division of parenchyma between segment 4A/B and left lateral segment induces accelerated hypertrophy of the remnant liver CT volumetry used to assess hypertrophy of left lateral segment Deportalized liver then removed	Allows for rapid (and possibly greater) hypertrophy in patients with inadequate hypertrophy following PVE or very small FLR	Morbidity, mortality, and oncologic outcomes relatively poor compared with more traditional strategies [27–29] Considered experimental and not performed in Toronto
Hepatic artery infusion (HAI) pump therapy [30–33]	Surgically placed catheter into hepatic artery with subcutaneous reservoir	HAI combined with systemic treatment can convert unresectable disease to resectable/ablatable disease in 25–50 % of patients compared with 10–30 % with systemic therapy alone	Requires multidisciplinary team with expertise in hepatobiliary surgery, medical oncology, interventional radiology, nuclear medicine, and nursing

(continued)

(continued)

	Technique	Advantage	Disadvantage
DEBIRI (drug-eluting bead, irinotecan) [34, 35]	Transarterial embolization with drug-eluting beads with irinotecan	Patients with unresectable hepatic disease who had DEBIRI had increased median OS of 7 months compared with FOLFIRI group ($p=0.031$, log-rank), with a sustained improvement in quality of life	Precise indications yet to be determined Not available at all centers
Irreversible electroporation (IRE)	Electric pulses cause permeabilization of membranes of tumor and parenchymal cells	Does not affect portal, biliary, or venous structures	Not used in patients with pacemakers or arrhythmias Requires general anesthesia
Stereotactic ablative radiotherapy (SABR/SBRT) [36]	Delivery of high doses of radiation to a focused target	Considered for patients deemed unresectable for patient or disease factors or those with larger hepatic metastases not otherwise ablatable Local control can be achieved in 85 % of patients at 3 years	Long term results not yet available Not offered at all centers
Transplantation [37–39]	Norwegian SECA study—cadaveric liver transplants for unresectable hepatic metastases, primary removed and no EHD	Calculated 5 year OS of 56 % for transplanted patients ($n=21$) and 44 % in the six patients who had progressive disease on last line of chemotherapy at the time of transplantation	Experimental
Yttrium-90 [40]	High-dose radiation delivered via the hepatic artery with microspheres	Could be used as salvage therapy for unresectable CRLM Median OS from administration of Y90 is 12 months	Short term restriction in patient exposure to friends/family due to radiation Not widely available

Landmark Publications

Synchronous CRLM

Clinical scenario	Study	Methods	Results
Simultaneous liver–colon vs. Staged Resection	Mayo Study Chua et al. [41]	Retrospective review $n=96$ Consecutive patients with synchronous CRLM	Simultaneous liver, colon resection had similar complication rates, but shorter overall hospital stay
	US Multicenter Study Reddy et al. [42]	Retrospective review $n=1085$ Patients with synchronous CRLM at three high volume US HPB centers	Simultaneous colon and major hepatectomy was associated with increased mortality and morbidity Simultaneous colon and minor hepatectomy is safe
	Memorial Sloan-Kettering Study Martin et al. [43]	Retrospective review $n=240$ Patients with synchronous CRLM	Less extensive resections undertaken in simultaneous liver–colon resection group, with lower rates of overall complications and length of stay

Bilobar Colorectal Metastases

Clinical scenario	Study	Methods	Results
Two-stage hepatectomy	French Study Jaeck et al. [44]	Retrospective review $n=33$ Patients with bilobar CRLM managed with two stage hepatectomies and PVE	Two-stage hepatectomy feasible in 75 % of patients with good long term survival
	Paul Brousse, Paris Study Adam et al. [7]	Retrospective review $n=59$ Patients with multiple CRLM treated with two stage hepatectomies, PVE ± ablation	Two-stage hepatectomy feasible in 69 % 5-year OS for those who completed both stages 42 %

PVE portal vein embolization, *CRLM* colorectal liver metastases, *OS* overall survival

Perioperative Chemotherapy in Resectable Liver Metastases

Clinical scenario	Study	Methods	Results
Perioperative chemotherapy for resectable liver metastases	EORTC Intergroup Trial Nordlinger et al. [45, 46]	RCT—Perioperative chemo + surgery vs. surgery alone	Perioperative chemotherapy (FOLFOX) increased progression free survival by 7.3 % at 3 years No difference in OS

RCT randomized controlled trial, *OS* overall survival

Preoperative Chemotherapy in Unresectable Liver Metastases

Clinical scenario	Study	Methods	Results
Conversion chemotherapy for unresectable liver metastases	CELIM Trial Folprecht et al. [47]	RCT Cetuximab + FOLFOX or FOLFIRI in unresectable CRLM	Chemotherapy with cetuximab increased response rates and resectability. Patients without KRAS mutations had a higher response rate
	UK Multicenter Study (BOXER) Wong et al. [48]	Prospective multicenter phase II single arm study Bevacizumab + CAPOX in unresectable CRLM	Bevacizumab + CAPOX increased response rates and resectability in patients with initially unresectable CRLM

CAPOX capecitabine + oxaliplatin, *CRLM* colorectal liver metastases, *RCT* randomized controlled trial

Liver and Extrahepatic Metastases

Clinical scenario	Study	Methods	Results
Surgical management of liver and pulmonary metastases	Toronto Liver and Pulmonary Resection Study for CRLM Shah et al. [49]	Retrospective review $n = 39$ Liver and pulmonary metastasectomies	DFS 19.8 months and overall survival 87 months after initial metastasectomy
Portal lymph node involvement	French Study Adam et al. [50]	Retrospective review $n = 47$ Liver resection and perihepatic lymphadenectomy (portal, celiac, retroperitoneal)	5-year survival higher for patients without LN involvement (18 % vs. 53 %) 5-year survival observed only in patients with hepatoduodenal LN (25 %), not in patients with celiac or retroperitoneal LN
Surgical management of EHM	International study, Pulitano et al. [6]	Retrospective review $n = 171$ Liver resection and EHM resection (lung, peritoneum, portal LN, aortocaval LN, other)	5-year survival for liver resection and EHM resection 26 % Overall survival worse with R1 resection, multiple sites of EHM and location (aortocaval nodes worst)

LN lymph node, *EHM* extrahepatic metastases, *DFS* disease-free survival

Referring to Medical Oncology

1. All patients should be seen by medical oncology.
2. Patients are often referred to surgery from medical oncology.

Referring to Radiation Oncology

1. Refer patients who are not candidates for surgery or other local therapies to be assessed for consideration of stereotactic radiation.

Referring to Multidisciplinary Cancer Conference (MCC)

1. Ideally, **all** CRLM should be reviewed.
2. Borderline resectable cases should be reviewed.
3. Patients who require a major hepatectomy and a major colorectal resection.
4. Patients with liver metastases and extrahepatic metastases.
5. Discuss timing of perioperative chemotherapy.

Toronto Pearls

- If there is any doubt about the volume of future liver remnant, obtain formal volumetrics and review at MCC. Consider preoperative portal vein embolization.
- Continue chemotherapy after Portal Vein Embolization (PVE) until resection to avoid growth of tumors.
- When performing liver resections, use the principle of parenchyma-sparing surgery as a guide.
- When performing liver resection after PVE, beware of distorted portal anatomy, especially shifted bile ducts.

References

1. Galandiuk S, et al. Patterns of recurrence after curative resection of carcinoma of the colon and rectum. Surg Gynecol Obstet. 1992;174(1):27–32.
2. Minagawa M, et al. Selection criteria for simultaneous resection in patients with synchronous liver metastasis. Arch Surg. 2006;141(10):1006–12.
3. Manfredi S, et al. Epidemiology and management of liver metastases from colorectal cancer. Ann Surg. 2006;244(2):254–9.

4. Adam R, et al. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004;240(4):644–57. discussion 657–8.
5. Beppu T, et al. Chemotherapy and targeted therapy for patients with initially unresectable colorectal liver metastases, focusing on conversion hepatectomy and long-term survival. Ann Surg Oncol. 2014;21 Suppl 3:S405–13.
6. Pulitano C, et al. Liver resection for colorectal metastases in presence of extrahepatic disease: results from an international multi-institutional analysis. Ann Surg Oncol. 2011; 18(5):1380–8.
7. Wicherts DA, et al. Long-term results of two-stage hepatectomy for irresectable colorectal cancer liver metastases. Ann Surg. 2008;248(6):994–1005.
8. Wei AC, et al. Survival after hepatic resection for colorectal metastases: a 10-year experience. Ann Surg Oncol. 2006;13(5):668–76.
9. Tomlinson JS, et al. Actual 10-year survival after resection of colorectal liver metastases defines cure. J Clin Oncol. 2007;25(29):4575–80.
10. Giuliante F, et al. Role of the surgeon as a variable in long-term survival after liver resection for colorectal metastases. J Surg Oncol. 2009;100(7):538–45.
11. Nordlinger B, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer. 1996;77(7):1254–62.
12. Fong Y, et al. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999;230(3):309–18.
13. Adams RB, et al. Selection for hepatic resection of colorectal liver metastases: expert consensus statement. HPB (Oxford). 2013;15(2):91–103.
14. Schiffman SC, et al. Laparoscopic versus open liver resection for metastatic colorectal cancer: a metaanalysis of 610 patients. Surgery. 2015;157:211–22.
15. Castaing D, et al. Oncologic results of laparoscopic versus open hepatectomy for colorectal liver metastases in two specialized centers. Ann Surg. 2009;250(5):849–55.
16. Nguyen KT, et al. Minimally invasive liver resection for metastatic colorectal cancer: a multiinstitutional, international report of safety, feasibility, and early outcomes. Ann Surg. 2009;250(5):842–8.
17. Gold JS, et al. Increased use of parenchymal-sparing surgery for bilateral liver metastases from colorectal cancer is associated with improved mortality without change in oncologic outcome: trends in treatment over time in 440 patients. Ann Surg. 2008;247(1):109–17.
18. Sarpel U, et al. Does anatomic versus nonanatomic resection affect recurrence and survival in patients undergoing surgery for colorectal liver metastasis? Ann Surg Oncol. 2009;16(2): 379–84.
19. de Rosa A, et al. Stage IV colorectal cancer: outcomes following the liver-first approach. J Surg Oncol. 2013;108(7):444–9.
20. Wang SC, D'Angelica MI. Chemotherapy-associated hepatotoxicity and hepatic resection for metastatic colorectal cancer. Curr Colorectal Cancer Rep. 2014;10(2):195–203.
21. Lee SJ, et al. Survival benefit from ovarian metastatectomy in colorectal cancer patients with ovarian metastasis: a retrospective analysis. Cancer Chemother Pharmacol. 2010;66(2):229–35.
22. Huang PP, et al. Long-term survival in patients with ovarian metastases from colorectal carcinoma. Ann Surg Oncol. 1998;5(8):695–8.
23. Gallinger S, et al. Liver resection for colorectal cancer metastases. Curr Oncol. 2013;20(3): e255–65.
24. Karanicolas PJ, et al. Long-term outcomes following tumor ablation for treatment of bilateral colorectal liver metastases. JAMA Surg. 2013;148(7):597–601.
25. Correa-Gallego C, et al. A retrospective comparison of microwave ablation vs. radiofrequency ablation for colorectal cancer hepatic metastases. Ann Surg Oncol. 2014;21:4278–83.
26. Schnitzbauer AA, et al. Right portal vein ligation combined with in situ splitting induces rapid left lateral liver lobe hypertrophy enabling 2-staged extended right hepatic resection in small-for-size settings. Ann Surg. 2012;255(3):405–14.

27. Oldhafer KJ, et al. ALPPS for patients with colorectal liver metastases: effective liver hypertrophy, but early tumor recurrence. World J Surg. 2014;38(6):1504–9.
28. Schadde E, et al. ALPPS offers a better chance of complete resection in patients with primarily unresectable liver tumors compared with conventional-staged hepatectomies: results of a multicenter analysis. World J Surg. 2014;38(6):1510–9.
29. Hernandez-Alejandro R, et al. Can we improve the morbidity and mortality associated with the associating liver partition with portal vein ligation for staged hepatectomy (ALPPS) procedure in the management of colorectal liver metastases? Surgery. 2015;157:194–201.
30. Goere D, et al. Prolonged survival of initially unresectable hepatic colorectal cancer patients treated with hepatic arterial infusion of oxaliplatin followed by radical surgery of metastases. Ann Surg. 2010;251(4):686–91.
31. Ammori JB, et al. Conversion to complete resection and/or ablation using hepatic artery infusional chemotherapy in patients with unresectable liver metastases from colorectal cancer: a decade of experience at a single institution. Ann Surg Oncol. 2013;20(9):2901–7.
32. D'Angelica MI, et al. Phase II trial of hepatic artery infusional and systemic chemotherapy for patients with unresectable hepatic metastases from colorectal cancer: conversion to resection and long-term outcomes. Ann Surg. 2015;261:353–60.
33. Karanicolas PJ, et al. Hepatic arterial infusion pump chemotherapy in the management of colorectal liver metastases: expert consensus statement. Curr Oncol. 2014;21(1):e129–36.
34. Richardson AJ, Laurence JM, Lam VW. Transarterial chemoembolization with irinotecan beads in the treatment of colorectal liver metastases: systematic review. J Vasc Interv Radiol. 2013;24(8):1209–17.
35. Fiorentini G, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32(4):1387–95.
36. Comito T, et al. Stereotactic Ablative Radiotherapy (SABR) in inoperable oligometastatic disease from colorectal cancer: a safe and effective approach. BMC Cancer. 2014;14:619.
37. Hagness M, et al. Liver transplantation for nonresectable liver metastases from colorectal cancer. Ann Surg. 2013;257(5):800–6.
38. Dueland S, et al. Chemotherapy or liver transplantation for nonresectable liver metastases from colorectal cancer? Ann Surg. 2015;261:956–60.
39. Dueland S, et al. Is liver transplantation an option in colorectal cancer patients with nonresectable liver metastases and progression on all lines of standard chemotherapy? Ann Surg Oncol. 2015;22:2195–200.
40. Saxena A, et al. A systematic review on the safety and efficacy of yttrium-90 radioembolization for unresectable, chemorefractory colorectal cancer liver metastases. J Cancer Res Clin Oncol. 2014;140(4):537–47.
41. Chua HK, et al. Concurrent vs. staged colectomy and hepatectomy for primary colorectal cancer with synchronous hepatic metastases. Dis Colon Rectum. 2004;47(8):1310–6.
42. Reddy SK, et al. Simultaneous resections of colorectal cancer and synchronous liver metastases: a multi-institutional analysis. Ann Surg Oncol. 2007;14(12):3481–91.
43. Martin R, et al. Simultaneous liver and colorectal resections are safe for synchronous colorectal liver metastasis. J Am Coll Surg. 2003;197(2):233–41.
44. Jaeck D, et al. A two-stage hepatectomy procedure combined with portal vein embolization to achieve curative resection for initially unresectable multiple and bilobar colorectal liver metastases. Ann Surg. 2004;240(6):1037–49.
45. Nordlinger B, et al. Perioperative chemotherapy with FOLFOX4 and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC Intergroup trial 40983): a randomised controlled trial. Lancet. 2008;371(9617):1007–16.
46. Nordlinger B, et al. Perioperative FOLFOX4 chemotherapy and surgery versus surgery alone for resectable liver metastases from colorectal cancer (EORTC 40983): long-term results of a randomised, controlled, phase 3 trial. Lancet Oncol. 2013;14(12):1208–15.

47. Folprecht G, et al. Tumour response and secondary resectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomised phase 2 trial. Lancet Oncol. 2010;11(1):38–47.
48. Wong R, et al. A multicentre study of capecitabine, oxaliplatin plus bevacizumab as perioperative treatment of patients with poor-risk colorectal liver-only metastases not selected for upfront resection. Ann Oncol. 2011;22(9):2042–8.
49. Shah SA, et al. Surgical resection of hepatic and pulmonary metastases from colorectal carcinoma. J Am Coll Surg. 2006;202(3):468–75.
50. Adam R, et al. Is hepatic resection justified after chemotherapy in patients with colorectal liver metastases and lymph node involvement? J Clin Oncol. 2008;26(22):3672–80.

Chapter 8
Gallbladder Cancer

Melanie E. Tsang, Natalie G. Coburn, and Paul F. Ridgway

Introduction

Gallbladder cancer (GBC) is relatively uncommon, with an incidence in North America of one to two people per 100,000. It is often found incidentally after an elective laparoscopic cholecystectomy. The main risk factors associated with the development of cancer include:

- Female–male (1.3–3.5:1) [1]
- History of gallstones/cholecystitis [2–7]
- Ethnic groups: Native American, Mexican, East Asian, Hispanic [8]
- Obesity and a high carbohydrate diet [9, 10]
- Anomalous pancreaticobiliary duct junction (APBDJ) [11, 12]
- Chronic GB infection (*S. typhi*) [13]
- Age (increased incidence) [14]
- Previous gastric surgery [15]

Unfortunately, less than 25 % of patients will present with resectable disease [16–19].

M.E. Tsang, M.D., M.Sc., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: melanie.tsang@mail.utoronto.ca

N.G. Coburn, M.D., M.P.H., F.R.C.S.C., F.A.C.S.
Department of Surgery, Sunnybrook Health Sciences Centre,
University of Toronto, Toronto, ON, Canada
e-mail: Natalie.Coburn@sunnybrook.ca

P.F. Ridgway, M.D., M.Med.Sc., F.R.C.S.I.
Department of Surgery, Trinity College Dublin at Tallaght Hospital, Dublin, Ireland
e-mail: PRidgway@rcsi.ie

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_8

Presentation (AJCC staging system)	Prognosis 5-year overall survival (OS) (%)
• Early (Stage 0–2)	60–100
• Advanced/regional (Stage 3A–4A)	4–13
• Metastatic (Stage 4B)	2

The recommended staging system is the International Union Against Cancer and American Joint Committee on Cancer (UICC/AJCC) 7th edition.

Definitions/Terminology

- **Anomalous pancreatic biliary duct junction (APBDJ)**: e.g., pancreatic joining common bile duct prior to the ampulla of Vater, causing a long common channel.
- **Extra hepatic bile duct (EHBD)**: portion of the bile duct that is extraneous to the liver and pancreas.
- **Simple cholecystectomy (SC)**: removal of the gallbladder and a portion of the cystic duct, performed laparoscopically or open. Simple cholecystectomy is conducted in a subserosal plane.
- **Radical cholecystectomy (RC)**: removal of the gallbladder including a subsegmental or segmental 4B/5 liver resection, removal of the portal/hepatoduodenal lymph nodes, and possible common bile duct excision (depending upon cystic duct margin status) with appropriate reconstruction.
- **Pancreaticoduodenectomy (PD)**: also known as a Whipple procedure, removal of the head of the pancreas, proximal jejunum, duodenum, antrum of stomach, gallbladder, cystic duct, common bile duct, and associated regional lymph nodes.
- **Radical resection**: involves removal of liver segments 4B/5, extending to include a formal lobectomy ± pancreaticoduodenectomy (depending upon extent of local invasion of tumor), with CBD removal [20].
- **Port/Trocar site metastases**: port site implantation at any of the port sites (not limited to the extraction site) was originally estimated to occur in 10–18 % cases after laparoscopic cholecystectomy [21]. More recent data suggest, however, the incidence of abdominal wall recurrence after laparoscopic procedure is low (7 %), comparable to open technique (5.1 %) [22]. Excision of port sites is controversial, as no survival advantage has been demonstrated to support routine removal [23]. Our recommendation is to consider removal in cases where bile spillage has occurred at the initial surgery or if the gallbladder was removed without a bag.
- **Role of frozen resection**: a negative frozen section of the cystic duct margin is mandatory during all radical cholecystectomies if the extrahepatic bile duct is not being resected.

Management

Different Scenarios and Presentations

Gallbladder polyps/adenoma	Incidental finding Intraoperative diagnosis/pathologic diagnosis	Suspected resectable GBC	Unresectable GBC
• History and physical exam • Ultrasound Imaging • Diagnostic workup should proceed as a suspected GBC if suggested by abnormal features on initial imaging • For polyps of a size ≥1 cm, surgery is advised • Consider laparoscopic cholecystectomy including cystic duct LN for 1–2 cm polyps, and the polyp position is favorable (on the contralateral wall to the bare area of the liver) • All specimens should be removed in a bag • Open cholecystectomy for larger polyps [24, 25] where preoperative imaging or intraoperative frozen section will dictate whether adjacent liver is removed en bloc	• 0.3–2 % of laparoscopic cholecystectomies • Intraoperative [1]: – Intraoperative staging – Frozen section of gallbladder – Remove cystic lymph node – Alert the pathologist as the specimen will be processed differently – Evaluate for definitive surgery, depending on surgeon experience and tumor resectability – If in doubt, close and refer to HPB Cancer Center • Pathologic: – History and physical exam – Pathology/operative note review – If T in situ or T1a, no further evaluation needed, surveillance only – If T1b or higher, Labs—liver function, Ca 19-9, CEA Imaging—CT Chest, Abdomen, Pelvis; MRI liver T1b—controversial; see Special Notes T2 and higher—Radical cholecystectomy	• History and physical exam • Labs: – Including liver function tests, Ca 19-9, CEA • Imaging: – CT chest and triphasic liver – MRI liver/MRCP • Consider staging laparoscopy (if ≥T2, equivocal imaging) • Consider decompression of biliary tree if jaundice present (see Special Notes) • Avoid biopsy if lesion is deemed surgically resectable **OPTIONAL**: • Consider EUS to assess extent of tumor involvement. Consider ERCP if drainage required (although frequently requires percutaneous trans-hepatic approach)	• History and physical exam • Labs: – Including liver function tests, Ca 19-9, CEA • Imaging: – CT chest, abdomen, pelvis – MRI/MRCP • Consider biopsy of distant disease (percutaneous) • Decompression if jaundice present (PTC with internalization, ERCP) • Medical/radiation oncology referral

GBC gallbladder cancer, *ERCP* endoscopic retrograde cholangiopancreatography, *EUS* endoscopic ultrasound, *PTC* percutaneous transhepatic cholangiography/catheter

Special Notes

- In Ontario, all patients with known or suspected GB cancer should be referred for management at a high volume hepatopancreatobiliary surgical oncology center.
- Bile spillage is estimated to occur in up to 20–40 % of elective laparoscopic cholecystectomy [26–28]. Bile spillage that has occurred during laparoscopic cholecystectomy in the setting of a high grade tumor should not delay or act as a deterrent for definitive surgery. Patients should be evaluated and treated according to the pathology of the tumor, and fitness of the patient for surgery, although they are likely at higher risk of recurrence.
- Further resection for T1b cancers has not been shown to improve overall survival, but may decrease rate of recurrence [26, 29]. In reasonable operative candidates, recommendation is to proceed with segment 4B/5 resection and lymphadenectomy.
- Jaundice is a poor prognostic marker (median disease-specific survival was 6 months vs. 16 months in non-jaundiced patients; no jaundiced patients were alive at 3 years). Surgical exploration may not be warranted in this patient population [30]
- Quality Indicators:
  - **Pathologic Review** should include location and size of tumor; depth of invasion; presence of perineural/vascular/lymphatic invasion; cystic duct node involvement; surgical margin status (particularly cystic duct margin); and evidence of perforation of gallbladder
  - **Operative Note** should include if gallbladder was removed intact; evidence of perforation or spillage of bile; excision of cystic node; removal of gallbladder using a bag with identification of the port site used; and use of wound protector

Management of Early Gallbladder Cancer

Scenario	Surgical management	Follow-up (F/U)
Tis or T1a (in situ or invades lamina propria only)	• Simple cholecystectomy • Radical cholecystectomy has not shown improved long term survival [24, 27] • LN metastases rare (2.5 %) [31]	• ESMO: should be restricted to history and physical examination tailored to symptoms

(continued)

(continued)

Scenario	Surgical management	Follow-up (F/U)
T1b (invades muscularis propria) (controversial; see Special Note) or T2 (penetrates perimuscular connective tissue, no extension beyond serosa or into liver)	• Radical cholecystectomy ± excision of port sites, with removal of cystic duct margin +/- CBD resection if involved (see Special Notes) • T1b: LN metastases 15–25 % for T1b [31, 32] • T2: LN metastases 20–62 % (portal node involvement), 20 % celiac and peripancreatic nodes for [20] • LN harvest recommended to include porta hepatis, gastrohepatic ligament, retroduodenal	• There is no evidence that regular follow-up after initial therapy influences outcome

LN lymph nodes, *ESMO* European Society of Medical Oncology

Special Notes

- Consider CBD resection if needed to obtain negative margins at all T stages
- Macroscopic recommended margins: 2 cm of adjacent liver tissue [28]
- Early re-exploration for patients with incidentally found T2 lesions [33]
- Initial studies show laparoscopic RC results in similar 5-year survival compared with open surgery [34]

Management of Advanced Gallbladder Tumors

Clinical scenario	Surgical management	Follow-up (F/U)
T3 (perforates serosa and/or directly invades the liver or other adjacent structure) T4 (invades main portal vein/hepatic artery or invades two or more extrahepatic structures)	• Radical hepatectomy (extended right, or right trisectionectomy) ± PVR if needed [28] (see note) • LN harvest recommended to include porta hepatic, gastrohepatic ligament, retroduodenal	• There is no evidence that regular follow-up after initial therapy may influence outcome

LN lymph nodes, *PVR* portal vein resection

Special Notes

- Adequacy of tumor resection (R0 status) rather than the extent of resection, predicts survival. Therefore, surgical resection should be tailored to obtaining complete oncologic clearance of the tumor and adequate lymphadenectomy [35].
- Extent of surgery for formal resection is determined by the location and stage of the tumor, as well as the intrahepatic anatomy and cystic duct margin.
- Right trisectionectomy is necessary for cancers involving the right hepatic artery and advanced lesions. PVE may be useful in these cases.

- Pancreaticoduodenectomy may be considered for distal lesions, although 5 year survival is reported at 9–10 % in two small series and median survival 21 months (one alive at 42 months) in another [36–38].
- The main limitation of a local (segment 4b/5) resection is the distance between the GB and the segment 8 portal pedicle, which can be as little as 2 mm away. Limited 4b/5 resections should only be considered in early lesions located in the fundus where an adequate (2 cm) margin can be obtained by ligation of the segment 5 portal pedicle with preservation of the segment 8 portal branches.
- Routine bile duct resection does not improve overall survival [39, 40]. Resection of the extrahepatic biliary duct (EHBD), however, is indicated in cases where the cystic duct margin is positive for cancer or high-grade dysplasia [41].
- EHBD resection is also indicated in cases with preoperative jaundice, cystic duct and Hartman's pouch cancers, as well as cases where resection of the EHBD is required to achieve adequate oncologic clearance due to proximity of GB and EHBD.

Unresectable/Metastatic Disease

Criteria of unresectability	Surgical management
• Metastatic disease: – To liver, lung, peritoneum, distant lymph nodes (N2: celiac, SMA nodes) • Patient factors: – Comorbidities rendering patient unable to tolerate potentially curative surgery • Anatomical factors: – There is no consensus for local extension of tumor that precludes resection. Tumor encasement of bilateral hepatic arteries or the common hepatic artery, however, is a contraindication to surgery	• Consider nonoperative approach to palliation if able (e.g., endoscopic stent/PTC placement) [42] • Palliative surgery only if nonoperative options are not possible

SMA superior mesenteric artery, *PTC* percutaneous transhepatic cholangiography/catheter

Landmark Publications

Prospective Randomized Control Trials (RCTs) regarding surgical management of this disease are few due to the relative rarity of the disease. Surgical management is largely dictated by consensus statements formed by high volume centers. Any reference to staging refers to the 7th edition of UICC staging.

Topic	Study	Methods	Results
Stage I: controversy	Wagholikar et al. [43]	• Retrospective review • $n=14$ patients • Early Stage • 12 patients treated with SC • 2 patients treated with RC	• Median survival: 42 months • 5-year OS 68 % • LR in 5/12 pts: all had T1b cancer treated with SC • T1a lesions can be treated with SC • Recommend T1b be treated with RC
	Wakai et al. [44]	• Retrospective review • $n=25$ patients • Patients with T1b cancer • 13 patients treated with SC • 12 patients treated with RC	• 10-year OS ($n=25$): 87 % • No difference in survival in patients with SC (100 %) vs. RC (87 %) • No LR in either group • T1b lesions can be treated with SC without impact on survival
Stage II	Taner et al. [45]	• Retrospective review • $n=131$ patients • 45 patients treated with SC • 60 patients treated with RC • 25 % patients had T2	• Median OS 11 months • RC associated with longer survival than SC (HR 0.42) for Grade T2 or higher • RC for patients with T2 tumors or greater (achieves longer term survival, whether administered as the initial surgery or after incidental discovery)
Stage III/IVA	Sasaki et al. [46]	• Retrospective review • $n=65$ patients • Advanced GBC • 27 patients with N1 disease • 6 underwent PD with hepatectomy	• Overall 5-year survival, N1 disease ($n=21$): 46.8 % • 16 pts recurred after curative OR (lymph node and distant metastases) • Surgical resection recommended only if R0 margin possible • High morbidity and mortality rates associated with extensive surgery, to be avoided in pts with para-aortic nodal disease

(continued)

(continued)

Topic	Study	Methods	Results
Medical oncology	UK-ABC-02 Valle et al. [47]	• RCT phase III, conducted in 37 centers in the UK • $n=410$ patients • Unresectable, recurrent, or metastatic biliary cancer (included intra/extrahepatic cholangiocarcinoma, ampullary, gallbladder cancer) • Two groups: Gemcitabine + Cisplatin or Gemcitabine alone for 24 weeks	• Median survival was 11.7 vs. 8.1 month for the Gem-Cis/Gem alone groups, respectively (HR 0.64, $p<0.001$) • Significant improvement in progression free survival, 8 months vs. 5 months Gem-Cis vs. Gem respectively (HR 0.63, $p<0.001$) • The combination of Gem-Cis chemotherapy for advanced/metastatic disease gave an average of 3.6 months longer life than gemcitabine alone, with limited toxicity, and represents an appropriate option for treatment in these patients
Radiation oncology	Kresl et al. [48]	• Retrospective review • $n=21$ patients (Stage III–IV) • Adjuvant CRT (5FU + EBRT 54 Gy)	• 5 years OS = 33 % (21 pts), 64 % if R0 resection with the addition of radiation • When compared to historical surgical control group, improved 5 years OS with R0 resection and addition of radiation (33 % vs. 64 %)

OS overall survival, *SC* simple cholecystectomy, *RC* radical cholecystectomy, *GBC* gallbladder cancer, *LR* locoregional recurrence, *PD* pancreaticoduodenectomy, *R0* negative microscopic margins, *CRT* chemoradiotherapy, *EBRT* external beam radiotherapy

Referring to Medical Oncology

1. All patients who are Stage II or higher (for consideration of adjuvant therapy, as part of a clinical trial or with Gemcitabine + Cisplatin). Adjuvant chemotherapy may also be considered for cancers with positive margins or lymphovascular invasion [49, 50].
2. All metastatic patients for consideration of palliative therapy.
3. Where possible, patients with gallbladder cancer should be considered for adjuvant trials.

Referring to Radiation Oncology

1. All patients who are T2 or higher, for consideration of adjuvant therapy (though there is limited evidence for this). Adjuvant treatment can be considered for R1 resection.
2. Palliative patients for consideration of symptomatic control.

Referring to MCC

1. All patient with T1b disease or higher.

Toronto Pearls

- All incidental T1b and higher cancers should be considered for re-resection. Aggressive surgery in early stage disease is associated with potential for cure.
- Laparoscopic radical cholecystectomy has been reported with reasonable oncologic outcomes, but the data are not robust enough for it to be routinely recommended [34, 51]
- Formal resection should be tailored to achieve complete oncologic (R0) clearance of the tumor.
- Limited resection (segment 4b/5) should be used selectively in T1b/T2 tumors located in the fundus where adequate tumor clearance can be achieved at the bifurcation of the right portal structures.
- Bile duct resection may be performed selectively based on cystic duct margin or oncologic clearance of the tumor.
- Portal lymphadenectomy should be performed for all cases T1b and higher.
- Adjuvant therapy should be considered for stage II disease and higher, ideally as part of a clinical trial.

References

1. Wernberg JA, Lucarelli DD. Gallbladder cancer. Surg Clin North Am. 2014;94(2):343–60.
2. Diehl AK. Epidemiology of gallbladder cancer: a synthesis of recent data. J Natl Cancer Inst. 1980;65(6):1209–14.
3. Lowenfels AB, et al. Gallstones and risk of gallbladder cancer. J Natl Cancer Inst. 1985;75(1):77–80.
4. Lowenfels AB, et al. Gallstone growth, size, and risk of gallbladder cancer: an interracial study. Int J Epidemiol. 1989;18(1):50–4.

5. Zatonski WA, et al. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. J Natl Cancer Inst. 1997;89(15):1132–8.
6. Lowenfels AB, et al. Epidemiology of gallbladder cancer. Hepatogastroenterology. 1999;46(27):1529–32.
7. Serra I, Diehl AK. Number and size of stones in patients with asymptomatic and symptomatic gallstones and gallbladder carcinoma. J Gastrointest Surg. 2002;6(2):272–3.
8. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer. 2006;118(7):1591–602.
9. Moller H, et al. Obesity and cancer risk: a Danish record-linkage study. Eur J Cancer. 1994;30A(3):344–50.
10. Calle EE, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.
11. Kimura K, et al. Association of gallbladder carcinoma and anomalous pancreaticobiliary ductal union. Gastroenterology. 1985;89(6):1258–65.
12. Nuzzo G, et al. Papillary carcinoma of the gallbladder and anomalous pancreatico-biliary junction. Report of three cases and review of the literature. Hepatogastroenterology. 2005;52(64):1034–8.
13. Dutta U, et al. Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. Am J Gastroenterol. 2000;95(3):784–7.
14. Misra S, et al. Carcinoma of the gallbladder. Lancet Oncol. 2003;4(3):167–76.
15. Caygill C, et al. Increased risk of biliary tract cancer following gastric surgery. Br J Cancer. 1988;57(4):434–6.
16. Alexander F, et al. Biliary carcinoma. A review of 109 cases. Am J Surg. 1984;147(4):503–9.
17. Oertli D, Herzog U, Tondelli P. Primary carcinoma of the gallbladder: operative experience during a 16 year period. Eur J Surg. 1993;159(8):415–20.
18. Wade TP, et al. Experience with distal bile duct cancers in U.S. Veterans Affairs hospitals: 1987–1991. J Surg Oncol. 1997;64(3):242–5.
19. de Groen PC, et al. Biliary tract cancers. N Engl J Med. 1999;341(18):1368–78.
20. Fong Y, Heffernan N, Blumgart LH. Gallbladder carcinoma discovered during laparoscopic cholecystectomy: aggressive reresection is beneficial. Cancer. 1998;83(3):423–7.
21. Wakai T, Shirai Y, Hatakeyama K. Radical second resection provides survival benefit for patients with T2 gallbladder carcinoma first discovered after laparoscopic cholecystectomy. World J Surg. 2002;26(7):867–71.
22. Paolucci V, Neckell M, Gotze T. Unsuspected gallbladder carcinoma--the CAE-S/CAMIC registry. Zentralbl Chir. 2003;128(4):309–12.
23. Maker AV, et al. Is port site resection necessary in the surgical management of gallbladder cancer? Ann Surg Oncol. 2012;19(2):409–17.
24. Koga A, et al. Diagnosis and operative indications for polypoid lesions of the gallbladder. Arch Surg. 1988;123(1):26–9.
25. Park JY, et al. Long-term follow up of gallbladder polyps. J Gastroenterol Hepatol. 2009;24(2):219–22.
26. Ouchi K, Mikuni J, Kakugawa Y. Laparoscopic cholecystectomy for gallbladder carcinoma: results of a Japanese survey of 498 patients. J Hepatobiliary Pancreat Surg. 2002;9(2):256–60.
27. Weiland ST, et al. Should suspected early gallbladder cancer be treated laparoscopically? J Gastrointest Surg. 2002;6(1):50–6.
28. Cleary SP, et al. Cancer of the gallbladder and extrahepatic bile ducts. Curr Probl Surg. 2007;44(7):396–482.
29. Lee SE, et al. Practical guidelines for the surgical treatment of gallbladder cancer. J Korean Med Sci. 2014;29(10):1333–40.
30. Hawkins WG, et al. Jaundice predicts advanced disease and early mortality in patients with gallbladder cancer. Ann Surg Oncol. 2004;11(3):310–5.
31. Ogura Y, et al. Radical operations for carcinoma of the gallbladder: present status in Japan. World J Surg. 1991;15(3):337–43.

32. Barreto SG, et al. Patterns of failure and determinants of outcomes following radical re-resection for incidental gallbladder cancer. World J Surg. 2014;38(2):484–9.
33. Muratore A, et al. Gallbladder cancer invading the perimuscular connective tissue: results of reresection after prior non-curative operation. J Surg Oncol. 2003;83(4):212–5.
34. Shirobe T, Maruyama S. Laparoscopic radical cholecystectomy with lymph node dissection for gallbladder carcinoma. Surg Endosc. 2015;29:2244–50.
35. Pawlik TM, et al. Incidence of finding residual disease for incidental gallbladder carcinoma: implications for re-resection. J Gastrointest Surg. 2007;11(11):1478–86. discussion 1486–7.
36. Nimura Y, et al. Hepatopancreatoduodenectomy for advanced carcinoma of the biliary tract. Hepatogastroenterology. 1991;38(2):170–5.
37. Wakai T, et al. Combined major hepatectomy and pancreaticoduodenectomy for locally advanced biliary carcinoma: long-term results. World J Surg. 2008;32(6):1067–74.
38. Doty JR, et al. Cholecystectomy, liver resection, and pylorus-preserving pancreaticoduodenectomy for gallbladder cancer: report of five cases. J Gastrointest Surg. 2002;6(5):776–80.
39. Choi SB, et al. Surgical strategy for T2 and T3 gallbladder cancer: is extrahepatic bile duct resection always necessary? Langenbecks Arch Surg. 2013;398(8):1137–44.
40. Wiggers JK, et al. Patterns of recurrence after resection of gallbladder cancer without routine extrahepatic bile duct resection. HPB (Oxford). 2014;16(7):635–40.
41. Shukla PJ, Barreto SG. Systematic review: should routine resection of the extra-hepatic bile duct be performed in gallbladder cancer? Saudi J Gastroenterol. 2010;16(3):161–7.
42. Baron TH. Expandable metal stents for the treatment of cancerous obstruction of the gastrointestinal tract. N Engl J Med. 2001;344(22):1681–7.
43. Wagholikar GD, et al. Early gallbladder cancer. J Am Coll Surg. 2002;194(2):137–41.
44. Wakai T, et al. Early gallbladder carcinoma does not warrant radical resection. Br J Surg. 2001;88(5):675–8.
45. Taner CB, Nagorney DM, Donohue JH. Surgical treatment of gallbladder cancer. J Gastrointest Surg. 2004;8(1):83–9.
46. Sasaki R, et al. Significance of extensive surgery including resection of the pancreas head for the treatment of gallbladder cancer--from the perspective of mode of lymph node involvement and surgical outcome. World J Surg. 2006;30(1):36–42.
47. Valle J, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med. 2010;362(14):1273–81.
48. Kresl JJ, et al. Adjuvant external beam radiation therapy with concurrent chemotherapy in the management of gallbladder carcinoma. Int J Radiat Oncol Biol Phys. 2002;52(1):167–75.
49. Nakamura M, et al. Gemcitabine-based adjuvant chemotherapy for patients with advanced gallbladder cancer. Anticancer Res. 2014;34(6):3125–9.
50. Horgan AM, et al. Adjuvant therapy in the treatment of biliary tract cancer: a systematic review and meta-analysis. J Clin Oncol. 2012;30(16):1934–40.
51. Cho JY, et al. Laparoscopic approach for suspected early-stage gallbladder carcinoma. Arch Surg. 2010;145(2):128–33.

Chapter 9
Desmoid Fibromatosis and Dermatofibrosarcoma Protuberans

Trevor D. Hamilton, Brendan Dickson, and Rebecca A. Gladdy

Introduction

Mesenchymal neoplasms with (myo)-fibroblastic differentiation include both benign and malignant entities; in addition, there are several distinct tumors with so-called "intermediate behavior" that can be locally aggressive and/or rarely metastasizing [1]. Within this category desmoid-type fibromatosis and dermatofibrosarcoma protuberans are most commonly encountered.

Desmoid-Type Fibromatosis

In contrast to its superficial counterpart—palmer/planter fibromatosis, desmoid-type fibromatosis (DF) typically occurs in the deep soft tissues. Tumors are characterized histologically by infiltrative fascicles of monomorphic spindle cells. The majority of tumors contain mutations in the β-catenin gene (*CTNNB1*) [2]. The annual incidence of DF is 2–4 per 1,000,000 individuals [3]. Most desmoids arise sporadically, although some may be associated with trauma or pregnancy.

T.D. Hamilton, M.D., F.R.C.S.C.
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
email: trevordhamilton@gmail.com

B. Dickson, M.D., M.Sc., F.C.A.P., F.R.C.P.C.
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
e-mail: BDickson@mtsinai.on.ca

R.A. Gladdy, M.D., Ph.D., F.R.C.S.C., F.A.C.S. (✉)
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: rgladdy@mtsinai.on.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_9

Approximately 5–10 % of patients with desmoids occur in patients that have Familial Adenomatous Polyposis (FAP) [4].

Dermatofibrosarcoma Protuberans

Dermatofibrosarcoma protuberans (DFSP) is a superficial neoplasm originating in the dermis or subcutis. Histologically it is characterized by storiform whorls of monomorphic spindle cells; however, progression to higher-grade "fibrosarcoma" (so-called fibrosarcomatous [FS-DFSP]) is associated with cytologic atypia and architectural transformation into a herringbone pattern. Greater than 90 % of tumors exhibit a translocation resulting in COL1A1-PDGFB gene fusion [5]. The annual incidence of DFSP is 1–4 per 1,000,000 individuals [6, 7]. It is most commonly seen between 20 and 50 years of age. DFSP has a propensity for local recurrence and rarely metastasis; however, following fibrosarcomatous transformation, which occurs in 5–15 % of DFSP patients, metastasis is seen in 10–15 % of cases [8]. The presence of a positive surgical margin significantly increases the risk of local recurrence in DFSP [9].

	Prognosis [9–17]	
Presentation	5-year overall survival (OS) (%)	5-year local recurrence (LR) (%)
DF	76[a]–100	20–47
DFSP	98–100	3–25

[a]Intra-abdominal DF in FAP patients—deaths due to complications of DF treatment or other causes

The American Joint Committee on Cancer AJCC 7th edition is the current recommended staging system for DFSP. DF is not included in the AJCC staging system as it is a benign neoplasm.

Management

Primary DF

There has been a shift in the management of DF in recent years from a frontline approach of surgical resection to a wait-and-see approach with a period of observation [18, 19]. Previous studies have demonstrated through multivariate analysis and predictive nomograms that age, tumor site and tumor size are independent risk factors for local recurrence after resection [20, 21]. Specific mutations in the β-catenin gene have also been found to be prognostic for local recurrence and may serve as biologic markers to guide management in the future [22, 23].

Clinical scenario	Workup	Management	Follow-up
Extra-abdominal and abdominal wall DF	History and physical exam Imaging: • MRI preferred Percutaneous core biopsy Pathologic assessment of ER/PR status in female patients Case discussion at MCC	Asymptomatic: • Trial of observation to assess growth rate • Consider trial of NSAIDs[a] or antiestrogens[b] if enlarging or large at presentation Symptomatic • Trial of NSAIDs or antiestrogens • Consider targeted agents[c] or cytotoxic chemotherapy[d] for larger lesions where surgical resection would confer considerable morbidity Indications for surgical resection: • Progressive disease despite medical therapy • Aim is for negative margins with preservation of function	History and physical exam every 3–6 months to establish pattern of growth MRI every 3–6 months for first 2 years, then annually if stable disease
Intra-abdominal DF	History and physical exam Imaging: • CT abdo/pelvis or • MRI Percutaneous core biopsy Pathologic assessment of ER/PR status in female patients Case discussion at MCC	Trial of observation if slow growth and asymptomatic. Otherwise consider medical therapy with NSAIDs, antiestrogens, targeted agents, or cytotoxic chemotherapy Indications for surgical resection: • Rapidly enlarging and encroaching on critical structures • Progressive disease despite medical therapy and symptomatic	History and physical exam every 3–6 months CT abdo/pelvis or MRI every 3–6 months for first 2 years, then annually if stable disease. Consider US if stable growth pattern

ER/PR estrogen receptor/progesterone receptor, *MCC* multidisciplinary cancer conference, *NSAIDs* nonsteroidal anti-inflammatory drugs, *US* ultrasound

[a]e.g., Sulindac, indomethacin

[b]e.g., Tamoxifen, raloxifene, toremifene

[c]e.g., Imatinib, sorafenib

[d]e.g., Doxorubicin, ifosfamide, dacarbazine, methotrexate plus vinca alkaloid

Special Notes

- **Recurrence**:
  - Recurrent DF should be managed in a similar fashion to primary DF with consideration to previous therapies, tumor location and biology
  - Patients with multiple recurrences after adequate resections should be considered for medical therapy
- **Margins**: The aim of surgical resection should be negative histologic margins with preservation of function. Despite this, 25 % of cases with negative margins

will recur locally. Unlike sarcomas, a positive surgical margin may not increase the risk of local recurrence [19, 20, 24, 25]

- **Medical therapy**:
  - NSAIDs—Response rates 57 % [26]
  - Antiestrogen therapy—Response rates 50 % [26]
  - Cytotoxic chemotherapy—Variable rates of partial response 19–100 % [27–29]

    Doxorubicin/dacarbazine
    Ifosfamide
    Methotrexate/vinblastine
    Vinorelbine
    Etoposide/cyclophosphamide

  - Targeted therapy—Imatinib response rates 16 % [30], Sorafenib response rates 25 % [31]
- **Regression**: Spontaneous regression has been reported in 19–28 % of cases [20, 32]; this is seen predominately in abdominal wall DF. This may reflect how different disease sites exhibit varying biology.
- **FAP**:
  - Younger patients with a new diagnosis of DF (especially abdominal) should be screened for FAP with sigmoidoscopy after obtaining a careful family history of colon cancer
  - FAP patients with DF have a higher rate of recurrence and nonsurgical options should be strongly considered prior to resection [11]
- **Pregnancy**:
  - Disease progression often occurs during pregnancy but can generally be managed safely with close observation with serial US in most cases [33]
  - The risk of adverse obstetric events is not increased in DF [33]
  - DF should not be a contraindication to future pregnancies [33]
  - Tumors arise in previous caesarian-section sites
- **Radiation Therapy**:
  - May be considered in patients with multiple local recurrences or unresectable disease but MCC discussion should be conducted prior to treatment [34]

Primary Localized DFSP

Workup	Management	Follow-up
History and physical exam MRI in selected cases—to assess depth/multifocality Preoperative biopsy	Surgical resection • Wide local excision (WLE) 2–3 cm Plastic surgery consultation if primary closure is anticipated to be challenging	History and physical exam every 6–12 months Re-biopsy of suspicious lesions MRI if any concerns

Special Notes

- **Recurrence**: Treat with surgical resection if possible
- **Imatinib:** Consider neoadjuvant imatinib for large, borderline resectable, or complex recurrent lesions in order to downsize prior to surgery
- **Margins**: Negative histologic margins should be the goal of surgical resection. There is debate in the literature on the appropriate margin width for wide local excision [35]
- **Resection**: Wide local excision is preferred. Mohs Micrographic Surgery is not recommended in the treatment of DFSP
- **Lymph nodes**: assessment of regional lymph nodes is not required in the absence of clinically apparent disease
- **FS-DFSP**: Approximately 10–15 % of DFSP contain fibrosarcomatous progression that behaves more aggressively (i.e., widespread metastasis) than classic DFSP [36]
- **Radiation Therapy**: May be useful adjuvant to surgery for large or recurrent tumors [37]

Metastatic DFSP

Workup	Management	Follow-up
History and physical exam CT chest/abdo/pelvis Case discussion at MCC	Systemic therapy with Imatinib Consider resection (lung, liver) if: • R0 resection can be achieved • Favorable biology (slow growing, long disease-free interval) • Primary tumor is resected or resectable • Isolated/few metastases Radiation therapy for unresectable, progressive, or bony metastases	As clinically warranted

Special Notes

- **Imatinib**: Can be used for unresectable, borderline resectable, recurrent or metastatic disease as >90 % of DFSP are characterized by the t(17;22) chromosomal translocation and may be susceptible to targeted platelet-derived growth factor inhibition [38].

Landmark Publications

There are no prospective randomized control trials (RCT) on the management of DF or DFSP. Management is largely dictated by consensus statements formed by large, high-volume centers.

DF

Study	Methods	Results
Ballo et al. [15]	Retrospective review *N* = 189 Patients treated with surgery, surgery and RT, or RT alone	Higher recurrence rate with positive margin (54 % vs. 27 % at 10 years) RT alone or in combination with surgery provided good local control (24 % and 25 % at 10 years)
Gronchi et al. [39]	Retrospective review *N* = 203 All patients treated with surgical resection All patients had complete macroscopic resection	DFS better in primary disease than recurrent disease (76 % vs. 59 % at 10 years)
Nieuwenhuis et al. [4]	Retrospective population-based review *N* = 519 All Dutch patients with DF over a 10 year period	7.5 % of DF associated with FAP Factors identified with FAP-associated DF: male, age < 60, intra-abdominal location
Salas et al. [20]	Multi-institution retrospective review *N* = 426 All patients had sporadic DF	Subgroup of patients treated with wait-and-see policy (19 % spontaneous remission) Age, tumor size, tumor site (extra-abdominal) predictive of PFS on multivariate analysis

RT radiation therapy, *DFS* disease-free survival, *PFS* progression-free survival

DFSP

Study	Methods	Results
Bowne et al. [9]	Retrospective review *N* = 159 All patients treated with WLE 16 % had DFSP-FS	Positive margins and FS-DFSP predictors of poor outcome 2 % of patients developed metastases and died of disease
Fiore et al. [16]	Retrospective review *N* = 218 All patients treated with WLE	Low rate of local recurrence at 5 years (3 %) Rate of distant metastases at 5 years (2 %)
Fields et al. [40]	Retrospective review *N* = 244 All patients treated with WLE	Depth and margin status predictive of DFS Low recurrence with WLE (92 % DFS at 5 years)

FS-DFSP DFSP with fibrosarcomatous transformation, *DFS* disease-free survival, *WLE* wide local excision

Referring to Medical Oncology

DF

1. Patients with abdominal (mesenteric) disease.
2. Patients with large tumors for whom surgical resection would be significantly morbid.
3. Patients with multiple local recurrences after surgical resection.
4. Patients with disease progression during observation.

DFSP

1. All patients with metastatic or unresectable disease.
2. Patients considered for neoadjuvant therapy to downstage.

Referring to Radiation Oncology

DF

1. Patients with multiple local recurrences for consideration of combined pre- or post-op treatment.
2. Patients with unresectable disease that has progressed on medical therapy.
3. Patients that would require extensively morbid resections.

DFSP

1. Patients with larger lesions or positive margins after maximal surgical resection.
2. Patients with DFSP-FS progression.

Referring to Multidisciplinary Cancer Conference (MCC)

DF

- All cases should be discussed.

DFSP

- All cases should be discussed.

Toronto Pearls

DF

- The biology and behavior of DF can be greatly varied between patients in terms of growth, stabilization, or regression. Treatment effects (i.e., antiestrogens, chemotherapy) may also take months to years to become apparent.
- Percutaneous core biopsies should ideally be done with image-guidance at sarcoma centers with specialized radiologists.
- Pathology review should ideally be done by expert pathologists experienced in sarcoma.
- DF is commonly seen in young patients and has no metastatic potential. Therefore, the strategy of surgical resection should focus on preservation of function to avoid significant morbidity.
- DF is rarely a cause for mortality except in large, recurrent abdominal tumors (particularly in FAP) or tumors located in the head and neck. Consequently, a multidisciplinary approach should be considered before embarking on extensive surgical resection.
- Debulking or incomplete resection of large tumors is not recommended.

DFSP

- Pathology review should ideally be done by expert pathologists experienced in sarcoma to accurately diagnose.
- Patients with DFSP-FS progression should be followed closely as they have a higher propensity for metastatic disease.
- Consider the use of imatinib in the neoadjuvant setting for locally advanced disease or in the management of metastatic disease.

References

1. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. WHO Classification of tumours of soft tissue and bone. 4th ed. Lyon, France: IARC; 2013.
2. Huss S, Nehles J, Binot E, et al. β-Catenin (CTNNB1) mutations and clinicopathologic features of mesenteric desmoid-type fibromatosis. Histopathology. 2013;62(2):294–304.

3. Reitamo JJ, Hayry P, Nykyri E, et al. The desmoid tumor I: incidence, sex-, age- and anatomical distribution in the Finnish population. Am J Clin Pathol. 1982;77(6):665–73.
4. Nieuwenhuis MH, Casparie M, Mathus-Vliegen LM, et al. A nation-wide study comparing sporadic and familial adenomatous polyposis-related desmoid-type fibromatoses. Int J Cancer. 2011;129:256–61.
5. Patel KU, Szabo SS, Hernandez VS, et al. Dermatofibrosarcoma protuberans COL1A1-PDGFB fusion is identified in virtually all dermatofibrosarcoma protuberans cases when investigated by newly developed multiplex reverse transcription polymerase chain reaction and fluorescence in situ hybridization assays. Hum Pathol. 2008;39:184–93.
6. Koh CK, Ko CB, Bury HP, et al. Dermatofibrosarcoma protuberans. Int J Dermatol. 1995;34(4):256–60.
7. Criscione VD, Weinstock MA. Descriptive epidemiology of dermatofibrosarcoma protuberans in the United States, 1973 to 2002. J Am Acad Dermatol. 2007;56(6):968–73.
8. Stacchiotti S, Pedeutour F, Negri T, et al. Dermatofibrosarcoma protuberans-derived fibrosarcoma: clinical history, biological profile and sensitivity to imatinib. Int J Cancer. 2011;129:1761–72.
9. Bowne WB, Antonescu CR, Leung DH, et al. Dermatofibrosarcoma protuberans: a clinicopathologic analysis of patients treated and followed at a single institution. Cancer. 2000; 88(12):2711–20.
10. Quintini C, Ward G, Shatnawei A, et al. Mortality of intra-abdominal desmoid tumors in patients with familial adenomatous polyposis: a single center review of 154 patients. Ann Surg. 2012;255:511–6.
11. Clark SK, Neale JC, Landgrebe JC, et al. Desmoid tumours complicating familial adenomatous polyposis. Br J Surg. 1999;86:1185–9.
12. Spear MA, Jennings LC, Mankin HJ, et al. Individualizing management of aggressive fibromatoses. Int J Radiat Oncol Biol Phys. 1998;40(3):637–45.
13. Lev D, Kotilingam D, Wei C, et al. Optimizing treatment of desmoid tumors. J Clin Oncol. 2007;25(13):1785–91.
14. Peng PD, Hyder O, Mavros MN, et al. Management and recurrence patterns of desmoids tumors: a multi-institutional analysis of 211 patients. Ann Surg Oncol. 2012;19:4036–42.
15. Ballo MT, Zagars GK, Pollack A, et al. Desmoid tumor: prognostic factors and outcome after surgery, radiation therapy, or combined surgery and radiation therapy. J Clin Oncol. 1999;17(1):158–67.
16. Fiore M, Miceli R, Mussi C, et al. Dermatofibrosarcoma protuberans treated at a single institution: a surgical disease with a high cure rate. J Clin Oncol. 2005;23(30):7669–75.
17. Chang CK, Jacobs IA, Salti GI. Outcomes of surgery for dermatofibrosarcoma protuberans. Eur J Surg Oncol. 2004;30:341–5.
18. Bonvalot S, Edlweny H, Haddad V, et al. Extra-abdominal primary fibromatosis: aggressive management could be avoided in a subgroup of patients. Eur J Surg Oncol. 2008;34:462–8.
19. Fiore M, Rimareix F, Mariani L, et al. Desmoid-type fibromatosis: a front-line conservative approach to select patients for surgical treatment. Ann Surg Oncol. 2009;16:2587–93.
20. Salas S, Dufresne A, Bui B, et al. Prognostic factors influencing progression-free survival determined from a series of sporadic desmoid tumors: a wait-and-see policy according to tumor presentation. J Clin Oncol. 2011;29(26):3553–8.
21. Crago AM, Denton B, Salas S, et al. A prognostic nomogram for prediction of recurrence in desmoid fibromatosis. Ann Surg. 2013;258(2):347–53.
22. Lazar AJF, Tuvin D, Hajibashi S, et al. Specific mutations in the β-catenin gene (CTNNB1) correlate with local recurrence in sporadic desmoid tumors. Am J Pathol. 2008;173(5): 1518–27.
23. Colombo C, Miceli R, Lazar AJ, et al. CTNNB1 45F mutation is a molecular prognosticator of increased postoperative primary desmoid tumor recurrence. Cancer. 2013;119:3696–702.
24. Cates JM, Stricker TP. Surgical resection margins in desmoid-type fibromatosis: a critical reassessment. Am J Surg Pathol. 2014;38(12):1707–14.

25. Gronchi A, Colombo C, Le Pechoux C, et al. Sporadic desmoid-type fibromatosis: a stepwise approach to a non-metastasising neoplasm – a position paper from the Italian and the French Sarcoma Group. Ann Oncol. 2014;25:578–83.
26. Janinis J, Patriki M, Vini L, et al. The pharmacological treatment of aggressive fibromatosis: a systematic review. Ann Oncol. 2003;14:181–90.
27. Garbay D, Cesne AL, Penel N, et al. Chemotherapy in patients with desmoid tumors: a study from the French Sarcoma Group (FSG). Ann Oncol. 2012;23:182–6.
28. de Camargo VP, Keohan ML, D'Adamo DR, et al. Clinical outcomes of systemic therapy for patients with deep fibromatosis (desmoid tumors). Cancer. 2010;116(9):2258–65.
29. Gega M, Yanagi H, Yoshikawa R, et al. Successful chemotherapeutic modality of doxorubicin plus dacarbazine for the treatment of desmoid tumors in association with familial adenomatous polyposis. J Clin Oncol. 2006;24(1):102–5.
30. Heinrich MC, McArthur GA, Demetri GD, et al. Clinical and molecular studies of the effect of Imatinib on advanced aggressive fibromatosis (desmoid tumor). J Clin Oncol. 2006;24(7): 1195–203.
31. Gounder MM, Lefkowitz RA, Keohan ML, et al. Activity of Sorafenib against desmoid tumor/ deep fibromatosis. Clin Cancer Res. 2011;17:4082–90.
32. Bonvalot S, Ternes N, Fiore M, et al. Spontaneous regression of primary abdominal wall desmoid tumors: more common than previously thought. Ann Surg Oncol. 2013;20:4096–102.
33. Fiore M, Coppola S, Cannell AJ, et al. Desmoid-type fibromatosis and pregnancy: a multi-institutional analysis of recurrence and obstetric risk. Ann Surg. 2014;259:973–8.
34. Gluck I, Griffith KA, Biermann JS, et al. Role of radiotherapy in the management of desmoid tumors. Int J Radiat Oncol Biol Phys. 2011;80(3):787–92.
35. Farma JM, Ammori JB, Zager JS, et al. Dermatofibrosarcoma protuberans: how wide should we resect? Ann Surg Oncol. 2010;17:2112–8.
36. Mendenhall WM, Zlotecki RA, Scarborough MT. Dermatofibrosarcoma protuberans. Cancer. 2004;101:2503–8.
37. Castle KO, Guadagnolo BA, Tsai CJ, et al. Dermatofibrosarcoma protuberans: long-term outcomes of 53 patients treated with conservative surgery and radiation therapy. Int J Radiat Oncol Biol Phys. 2013;86(3):585–90.
38. McArthur GA, Demetri GD, van Oosterom A, et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imatinib: imatinib target exploration consortium study B2225. J Clin Oncol. 2005;23(4):866–73.
39. Gronchi A, Casali PG, Mariani L, et al. Quality of surgery and outcome in extra-abdominal aggressive fibromatosis: a series of patients surgically treated at a single institution. J Clin Oncol. 2003;21(7):1390–7.
40. Fields RC, Hameed M, Qin L, et al. Dermatofibrosarcoma protuberans (DFSP): predictors of recurrence and the use of systemic therapy. Ann Surg Oncol. 2011;18:328–36.

Chapter 10
Gastric Adenocarcinoma

Gareth Eeson, Savtaj S. Brar, and Natalie G. Coburn

Introduction

In 2014, the Canadian Cancer Society estimated gastric adenocarcinoma to be the 14th most commonly diagnosed malignancy, with 3300 new cases and 2100 deaths. The age-standardized incidence and mortality rate for gastric cancer have decreased from 19.0/100,000 cases and 15.5/100,000 deaths in 1980 to 9.1/100,000 and 4/100,000 deaths, respectively, in 2014 [1]. Established risk factors for gastric cancer include *H. pylori* infection, smoking, alcohol, and dietary factors. Hereditary gastric cancers are seen in the Lynch syndrome and hereditary diffuse gastric cancer (HDGC) but represent <5 % of all gastric cancers. Enormous geographic variation in the incidence of gastric cancer exists with the highest incidence being observed in East Asia. Similarly, wide geographic variation in treatment outcomes is observed with overall 5-year survival rates of 40–60 % reported in Asia and Europe, compared to 21 % in Canada [1, 2].

G. Eeson, M.D., M.Sc., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: gareth.eeson@sunnybrook.ca

S.S. Brar, M.D., M.Sc., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: sbrar@mtsinai.on.ca

N.G. Coburn, M.D., M.P.H., F.R.C.S.C., F.A.C.S.
Department of Surgery, Sunnybrook Health Sciences Centre,
University of Toronto, Toronto, ON, Canada
e-mail: Natalie.Coburn@sunnybrook.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_10

Stage	5-Year overall survival (OS) [3, 4][a]
• Stage I	57–71 %
• Stage II	33–46 %
• Stage III	9–20 %
• Stage IV	4 %

[a]North American survival data

Gastric adenocarcinomas are classified histologically according to the Lauren classification as (1) intestinal or (2) diffuse histologic subtypes [5]. Staging of gastric adenocarcinoma is according to the American Joint Committee on Cancer 7th edition. Tumors arising within 5 cm of the gastroesophageal junction with extension into the esophagus are classified, staged, and treated as esophageal cancers [6].

Definitions/Terminology

- **Early Gastric Cancer (EGC)**: tumors confined to the mucosa (Tis or T1a), independent of the presence of lymph node involvement. EGC is predominately identified by subtle changes in color, vascularity, or texture and is rarely diagnosed outside areas where population-based screening is offered such as Japan and Korea.
- **Advanced Gastric Cancer (AGC):** T1b to T4 (invading submucosa, muscularis propria, subserosa, perforating serosa, or invading adjacent structures), without distant metastasis.
- **Endoscopic Mucosal Resection (EMR):** employs endoscopic techniques to elevate (e.g., injection, suction) and resect (e.g., cautery, banding) mucosal lesions en bloc
- **Endoscopic Submucosal Dissection (ESD):** is a variation of EMR that employs submucosal injection and a specialized needle-knife to permit en bloc resection of mucosal and submucosal lesions.
- **Subtotal Gastrectomy (SG):** removal of 1/2 to 3/4 of the gastric tissue, including omentum and all associated lymph nodes appropriate for a D1 or D2 lymphadenectomy. For distal gastric cancers, SG has been shown to have an equivalent oncological outcome and lesser morbidity when compared to total gastrectomy. SG is also associated with a better nutritional status and quality of life [7].
- **Total Gastrectomy (TG):** removal of all of the gastric tissue and distal esophagus, including omentum and all associated lymph nodes appropriate for a D1 or D2 lymphadenectomy. TG is preferred for tumors confined to the proximal 1/3 of the stomach.
- **Palliative Gastrectomy (PG):** gastrectomy performed with the intent to alleviate symptoms from the primary gastric cancer in the context of metastatic disease. A gastrectomy performed otherwise in a patient with metastatic disease is considered a non-curative gastrectomy [8].

- **D1 Lymph Node Dissection**: includes removal of the omentum with perigastric lymph nodes (stations 1–6) and lymph nodes along the left gastric artery (station 7). Station 2 is not removed for SG [9].
- **D2 Lymph Node Dissection**: D1 nodes and lymph nodes along the common hepatic artery (station 8a), celiac axis (station 9), splenic artery (stations 10 and 11), and hepatic artery proper (station 12a) [9]. Clearance of station 10 and 11 nodes may require splenectomy (See Special Notes - Extent of Lymphadenectomy) (Fig. 10.1) [10].

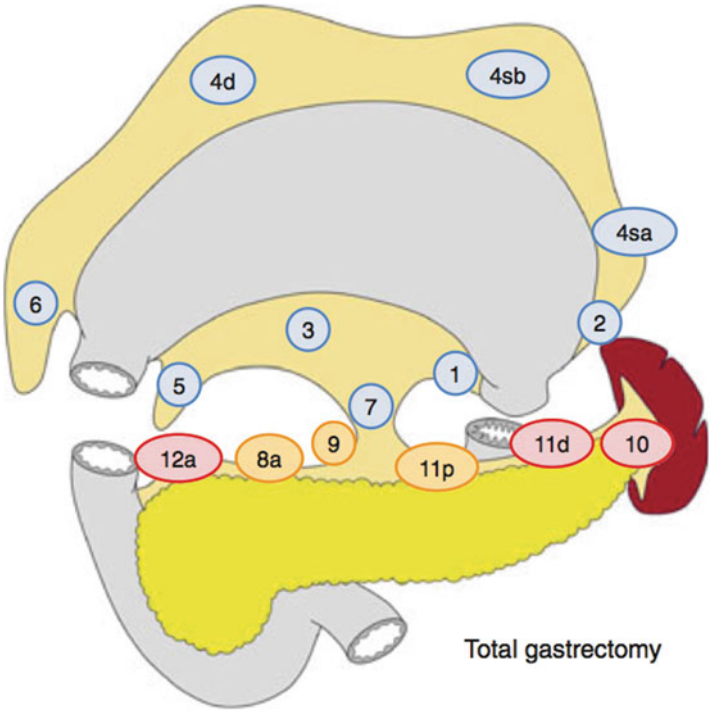


Fig. 10.1 Gastric lymph node stations

Management

Early Gastric Cancer (EGC)

Work-up	Surgery	Adjuvant therapy	Follow-up (F/U)
Recommended Tests: • History and physical exam • Upper endoscopy • Imaging: – CT abdo/pelvis – EUS • Staging laparoscopy[a] **Optional Tests:** • CT chest • PET is not indicated for EGC	• **Gastrectomy** with D1 lymph node dissection[a] OR • **Endoscopic resection** can be considered for lesions fulfilling all of the following [11][a]: – Intestinal type – Confined to mucosa (Tis or T1a) and cN0 – Elevated lesions <20 mm or flat lesions <10 mm in diameter – Absence of high-risk features (ulceration, poorly differentiated, lymphovascular invasion)	• Indicated for all node-positive disease	• Every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years, and yearly thereafter with: – History and physical exam – B12, Fe, bone density if TG was performed **Optional Tests:** • CT abdo/pelvis[a] • EGD[a]

EGC early gastric cancer, *EUS* endoscopic ultrasound, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *SG* subtotal gastrectomy, *TG* total gastrectomy, *RCT* randomized controlled trials, *EGD* esophago-gastro duodenoscopy
[a]See Special Notes

Special Notes: Early Gastric Cancer

- Endoscopic resection: Robust evidence comparing EMR/ESD to gastrectomy is lacking and gastrectomy remains the current standard of care [12]. EMR/ESD may be used in appropriately selected lesions amenable to en bloc resection that have minimal or no risk of nodal metastasis by experienced providers. Expanded criteria for ESD outside of the criteria listed above are considered investigational.
- Staging laparoscopy: Limited use in EGC. In cases where the tumor is reliably felt to be clinically T1 or T2 and NO, then SL can be omitted.
- Extent of lymphadenectomy: Considerable controversy surrounds the role of extended lymphadenectomy (D1 vs. D2 resection) in gastric cancer. Adequate staging requires 16 or more lymph nodes to be harvested. For cT1N0 tumors D1 with splenopancreatic preservation is generally recommended. Worse outcomes have been associated with D2 lymphadenectomy in patients with EGC [13].
- Resection margin: Positive microscopic margins are associated with an inferior survival to those in whom R0 status was achieved for EGC. A gross margin of 4 cm or greater is recommended for T1b–T3 tumors to ensure an R0 resection [14, 15].

- Laparoscopic gastrectomy (LG): LG is appropriate for EGC in experienced, high-volume centers [16]. Improved short-term outcomes have been demonstrated with LG, but oncologic outcomes are currently being evaluated with ongoing RCTs [17].
- Follow-up surveillance:
  - Evidence to support the benefit of early detection of recurrence is lacking. Most providers perform surveillance with serial CT scans.
  - Surveillance EGD should be offered to patients at risk of local recurrence (e.g., following endoscopic resection) when completion gastrectomy would be considered.

Advanced Gastric Cancer (Non-metastatic)

Work-up	Surgery	Adjuvant therapy	Follow-up (F/U)
Recommended Tests: • History and physical exam • Upper endoscopy • Imaging: – CT abdo/pelvis • Staging laparoscopy[a] **Optional Tests**: • CT chest • EUS[a] • PET is not indicated	• **Gastrectomy** with D1 or D2 lymphadenectomy – SG or TG depending on location of tumor[a] – Consider intraoperative margin assessment[a] • Multivisceral resection should be performed if the patient is considered a candidate for curative resection	• The two standard regimens are: – Perioperative ECF [18] **OR** – Postoperative 5-FU-based CRT[19] • There is no evidence that either regimen is superior to the other, but each has been shown to be superior to resection alone in RCT [20] *See adjuvant section*	• Every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years, and yearly thereafter with: – History and physical exam – B12, Fe, bone density if TG was performed **Optional Tests:** • CT abdo/pelvis[a] • EGD[a]

EUS endoscopic ultrasound, *SG* subtotal gastrectomy, *TG* total gastrectomy, *RCT* randomized controlled trial, *ECF* epirubicin, cisplatin and fluorouracil 5-FU, *CRT* chemoradiotherapy, *EGD* esophago-gastro duodenoscopy

[a]See Special notes

Special Notes: Advanced Gastric Cancer

- Staging laparoscopy: Radiologically occult peritoneal metastases are found in 20–30 % of patients with T2 or higher disease [21]. SL is indicated in patients with a high risk of peritoneal metastasis not seen with standard imaging (typically T3 or higher). Patients with positive peritoneal washings experience outcomes comparable to those with overt metastatic disease and should be considered palliative [22].
- Endoscopic ultrasound (EUS): EUS is valuable in the distinction between EGC and AGC and is critical if considering EMR/ESD. In patients with an established diagnosis of AGC, EUS is unlikely to change management and is not routinely required.

- Intraoperative margin assessment (i.e., frozen section): Can assist with achieving R0 resection if further resection can be safely performed, particularly for tumors with greater depth of invasion or diffuse histology. Consensus recommendations support selective use of intraoperative frozen section if gross margin <5 cm or for T3/T4 tumors [16].
- Extent of lymphadenectomy: Evidence suggests improved cancer-specific outcomes with D2 resection, particularly in higher staged tumors (T2-4) [13, 23]. Splenopancreatectomy is clearly associated with higher operative morbidity and is avoided unless required to achieve R0 resection margins [9]. Involvement of nodes beyond a D2 resection (i.e., mesenteric, para-aortic, retroperitoneal) is classified as distant metastases [6]. The role of "D3" resections is not supported in the management of gastric cancer [24].
- Bursectomy: (removal of the anterior leaflet of the transverse mesocolon and the pancreatic capsule along with total omentectomy) is routinely performed for serosa-positive gastric cancers according to Japanese guidelines, but the clinical benefit remains uncertain and is being examined in the JCOG 1001 trial [25]. Bursectomy can be considered for posterior T3/T4a tumors [10, 25, 26].
- Laparoscopic gastrectomy (LG): LG is not recommended for AGC due to limited available evidence on oncologic outcomes [10, 16]. An ongoing Korean RCT is investigating oncologic outcomes of LG in AGC [27].

Unresectable or Metastatic Gastric Cancer

Work-up	Management	Follow-up (F/U)
Recommended Tests: • History and physical exam • Upper endoscopy • HER-2 status • Imaging: – CT abdo/pelvis **Optional Tests:** – Staging laparoscopy[a] – CT chest	• Consider chemotherapy, radiotherapy, and nonoperative management for symptomatic patients. • Palliative gastrectomy should be avoided, and only performed for severely symptomatic patients, for whom all nonsurgical options have been exhausted[a]. • Stenting is associated with less morbidity than resection or bypass for palliation of obstruction and is typically preferred • Radiation or angioembolization can be effective for transfusion-dependent bleeding	• As symptoms warrant

[a]See Special Notes

Special Notes: Unresectable or Metastatic Gastric Cancer

- Staging laparoscopy: may have utility in confirming metastatic disease, especially carcinomatosis, if suspected on imaging. No role in the setting of confirmed metastatic disease.

- Criteria for nonoperative management
  - Unresectable
    - Level 3 or 4 suspicious nodes on imaging or confirmed by biopsy. Level 3 nodes include the posterior surface of the pancreas (nodal station 13), superior mesenteric artery, and vein (station 14). Level 4 nodes are middle colic vessels (station 15) and the para-aortic nodes (station 16).
    - Invasion or encasement of major vascular structures, such as celiac axis and its branches, is considered unresectable. Isolated left gastric artery involvement can be treated with curative intent if an R0 margin is obtainable.
  - Metastatic spread or peritoneal seeding (including positive peritoneal cytology) identified at surgical resection is considered incurable. Unless symptoms exist, systemic therapy should be considered rather than resection.
  - Non-curative gastrectomy has been demonstrated to impart no benefit in the setting of metastatic disease and exposes patients to unnecessary surgical procedures and risks of complications [28].

Landmark Surgical Publications (D1 vs. D2 Lymphadenectomy)

Study	Methods	Results
Dutch Trial Bonenkamp et al. [29]	• RCT • $N=711$ • D1 vs. D2 resection (D2 resection included distal pancreatectomy and splenectomy)	• Morbidity: 43 % D2 vs. 25 % D1 ($p<0.001$) • Mortality: 10 % D2 vs. 4.0 % D1 ($p=0.004$) • Median postoperative stays: D2 25 days vs. D1 18 days; $p<0.001$ 5-year update [9]: • No difference in 5-year OS rates: 35 % D1 vs. 33 % D2 15-year update [23]: • Overall 15-year survival: 22 % D1 vs. 28 % D2; $p=0.34$ • Deaths from gastric cancer: 48 % D1 vs. 37 % D2; $p=0.01$
Medical Research Council (MRC) ST01 Cuschieri et al. [30]	• RCT • $N=400$ • D1 vs. D2 resection (D2 resection includes distal pancreatectomy and splenectomy)	• Morbidity: 46 % D2 vs. 28 % D1; $p<0.001$ • Mortality: 13 % D2 vs. 6.5 % D1; $p=0.04$ 5-year update [31]: • No difference in 5-year OS rates: 35 % D1 vs. 33 % D2

(continued)

(continued)

Study	Methods	Results
Italian Gastric Cancer Surgical Group (IGCSG) Degiuli et al. [32]	• RCT • *N* = 267 • D1 vs. D2 resection • In the D2 arm, spleen and pancreas were preserved unless direct tumor extension. Splenectomy was performed for T1 or higher tumors on the greater curvature of the proximal or middle 1/3 of the stomach	• No difference in 5-year OS: 66.5 % D1 vs. 64.2 % D2 • Morbidity: 10.5 % D1 vs. 16.3 % D2; $p < 0.29$ • In-hospital mortality: 0 % D2 vs. 1.3 % D1; not statistically significant 5-year update [13]: • Trend towards improved 5-year OS for advanced disease (T2-4; N+): 59 % D2 vs. 38 % D1; $p = 0.055$

CRT chemoradiotherapy, *OS* overall survival, *RCT* randomized control trial

Landmark Chemotherapy and Chemoradiation Publications

Study	Methods	Results
INT-0116 Trial MacDonald et al. [19]	• RCT • *N* = 556 • Surgery plus adjuvant CRT vs. surgery alone • Adjuvant treatment was 5-FU + leucovorin followed by 4500 cGy • All patients received curative-intent surgery: – Only 10 % received D2 resection – 54 % received D0 resection	• **Improved overall and relapse-free survival with adjuvant CRT** • Median OS: 36-month CRT vs. 27-month surgery alone; $p = 0.005$ • Median RFS: 30-month CRT vs. 19-month surgery alone; $p < 0.001$ • 3-year OS: 50 % CRT vs. 41 % surgery alone; $p = 0.005$
MAGIC Trial Cunningham et al. [18]	• RCT • *N* = 503, T2 or higher • Surgery with perioperative ECF vs. surgery alone • ECF was administered for 3 cycles preoperatively and 3 cycles postoperatively	• **Improved PFS and OS with perioperative ECF** • 5-year OS: 36 % ECF vs. 23 % surgery alone; HR 0.75 (95 % CI 0.60–0.93), $p = 0.009$ • PFS: HR 0.66 (95 % CI 0.53–0.81), $p < 0.001$
GASTRIC Study Paoletti et al. [33]	• Patient-level meta-analysis of 17 RCTs • *N* = 3838 • Chemotherapy after complete resection vs. surgery alone	• **Improved OS and DFS with adjuvant chemotherapy in resectable gastric cancer** • OS: HR = 0.82 (95 % CI 0.76–0.90; $P < 0.001$) • DFS : HR = 0.82 (95 % CI 0.75–0.90; $P < 0.001$)

(continued)

(continued)

Study	Methods	Results
CLASSIC Trial Noh et al. [34]	• Multicenter RCT • $n=1035$ pts., stage II–IIIB • Surgery plus adjuvant capecitabine and oxaliplatin vs. surgery alone All pts underwent D2 resection	• **Improved DFS and OS with chemo** • 5-year DFS : 68 vs. 53 %; HR 0.58 (95 % CI 0.47–0.72) • 5-year OS : 78 vs. 69 %; HR 0.66 (95 % CI 0.51–0.85)
ARTIST-I Trial Park et al. [35, 36]	• RCT • $n=458$ • All patients underwent D2 gastrectomy • Chemotherapy alone (6 cycles capecitabine + cisplatin) vs. CRT (4 cycles chemo; 45 Gy with concurrent capecitabine)	• **No difference in DFS and OS @ 7-years median follow-up** • 5-year DFS : HR 0.74 (95%CI 0.52–1.05; $p=0.092$) • 5-year OS : 73 vs. 75 %, HR 1.13 (95 %CI 0.78–1.65; $p=0.53$) • Subgroup analysis suggests benefit of CRT for node-positive disease and intestinal subtype (awaiting results of ARTIST-II trial)

CRT chemoradiotherapy, *OS* overall survival, *RFS* relapse-free survival, *PFS* progression-free survival, *DFS* disease-free survival, *HR* hazard ratio, *RCT* randomized control trial, *ECF* epirubicin/cisplatin/5-fluorouracil

Landmark Palliative Publications

Study	Methods	Results
Chemotherapy vs. best supportive care in non-curable gastric cancer Glimelius et al. [37]	• RCT • $N=61$, unresectable • Chemotherapy + best supportive care vs. best supportive care alone • Chemotherapy was ELF-regimen consisting of 5-fluorouracil, leucovorin, and etoposide	• **Improved or prolonged high-quality life at 4 months**: 45 % chemotherapy group vs. 20 % best supportive care group; $p<0.05$
TOGA Trial Bang et al. [38]	• RCT • $N=584$, inoperable or metastatic, HER-2+ gastric cancer • Chemotherapy alone (capecitabine or 5-FU + cisplatin) vs. chemotherapy + trastuzumab	• **Improved median OS in HER2+ patients treated with trastuzumab**: median OS 13.8-month trastuzumab vs. 11.1-month chemotherapy alone ($p=0.0046$) • 22 % of patients assessed were HER2+

(continued)

(continued)

Study	Methods	Results
REGATTA Trial Fujitani K et al., 2016 [28]	• RCT • *N* = 175 (planned *N* = 330) • Eligibility: gastric cancer (cT1-3), single non-curable site of disease confined to liver, peritoneum or para-aortic lymph node, PS 0-1 • Gastrectomy (D1 without resection of metastases) followed by chemotherapy (S-1 plus cisplatin) vs. chemotherapy alone	• **Terminated early by DSMC based on futility:** 2 yr OS 25.1 % for gastrectomy followed by chemotherapy vs. 31.7 % for chemotherapy alone (p = 0.68)

OS overall survival, *RCT* randomized control trial, *5-FU* fluorouracil; *PS* performance status; *DSMC* data safety monitoring committee

Referring to Medical Oncology and Radiation Oncology

- Strong evidence exists supporting the role of adjuvant therapy in addition to surgical resection [19, 33]. The two standard regimens most frequently offered are perioperative ECF (epirubicin, cisplatin, and fluorouracil 5-FU) [18], or post-operative 5-FU and radiation [19]. There is no evidence that either regimen is superior.
- As the decision regarding adjuvant treatments should be made preoperatively, all patients should be referred to medical oncology and radiation oncology prior to resection and discussed at a multidisciplinary care conference.
- Relative contraindications to chemotherapy [20]
  - Impaired cardiac function such as congestive heart failure, baseline left ventricular ejection fraction less than 50 %, transmural myocardial infarction, valvular heart disease, high-risk arrhythmias
  - Impaired renal function (Cr clearance of <60 ml/min)
  - Disorders of the nervous system and diabetes are relative contraindications for chemotherapy with neuropathic agents (e.g., platinums)
- Relative contraindications to radiation
  - Prohibitive toxicities anticipated due to volume or adjacent structures
  - Connective tissue disease
  - Previous irradiation to area

Referring to Multidisciplinary Cancer Conference

- All cases of advanced gastric cancer should be discussed at a Multidisciplinary Cancer Conference (MCC), before surgical intervention to devise an individual plan for each patient.
- Gastric cancer cases that were not discussed at MCC preoperatively should be discussed if the final pathology is >T1N0.

References

1. Canadian Cancer Society. Canadian Cancer Society's Steering Committee: Canadian Cancer Statistics 2014. Toronto: Canadian Cancer Society; 2014.
2. Kim JP. Surgical results in gastric cancer. Semin Surg Oncol. 1999;17(2):132–8.
3. Kim JP, Hur YS, Yang HK. Lymph node metastasis as a significant prognostic factor in early gastric cancer: analysis of 1,136 early gastric cancers. Ann Surg Oncol. 1995;2(4):308–13.
4. Survival rates for stomach cancer, by stage. [cited 2014 November 1]; Available from: http://cancer.org/Cancer/StomachCancer/DetailedGuide/stomach-cancer-survival-rates.
5. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
6. Edge S, Byrd D, Compton C, Fritz A, Greene F, Trotti A. American Joint Committee on cancer staging manual. New York: Springer; 2009.
7. Gouzi JL, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. Ann Surg. 1989;209(2):162–6.
8. Mahar AL, et al. A systematic review of surgery for non-curative gastric cancer. Gastric Cancer. 2012;15 Suppl 1:S125–37.
9. Bonenkamp JJ, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med. 1999;340(12):908–14.
10. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113–23.
11. Gotoda T. Endoscopic resection of early gastric cancer: the Japanese perspective. Curr Opin Gastroenterol. 2006;22(5):561–9.
12. Bennett C, Wang Y, Pan T. Endoscopic mucosal resection for early gastric cancer. Cochrane Database Syst Rev. 2009;4:CD004276.
13. Degiuli M, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg. 2014;101(2):23–31.
14. Kim SH, et al. Effect of microscopic resection line disease on gastric cancer survival. J Gastrointest Surg. 1999;3(1):24–33.
15. Gastric Cancer, in NCCN Clinical Practice Guidelines in Oncology 2015. National Comprehensive Cancer Network. NCCN Clinical Practice Guideline in Oncology Gastric Cancer v3.2015. http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf
16. Brar S, et al. Defining surgical quality in gastric cancer: a RAND/UCLA appropriateness study. J Am Coll Surg. 2013;217(2):347–57. e1.
17. Kim W, et al. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-term Outcomes From a Multicenter Randomized Controlled Trial (KLASS-01). Ann Surg. 2015;263(1):28–35.
18. Cunningham D, et al. Perioperative chemotherapy versus surgery alone for resectable gastro-esophageal cancer. N Engl J Med. 2006;355(1):11–20.

19. Macdonald JS, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10): 725–30.
20. Knight G, Earle CC, Cosby R, Coburn N, Youssef Y, Spithoff K, Malthaner R, Wong RKS, The Gastrointestinal Cancer Disease Site Group. Neoadjuvant or adjuvant therapy for resectable gastric cancer, Evidence-based series 2-14 version 3.2011. Toronto: Cancer Care Ontario; 2011.
21. Lowy AM, et al. Laparoscopic staging for gastric cancer. Surgery. 1996;119(6):611–4.
22. Oh CA, et al. Long-term results and prognostic factors of gastric cancer patients with only positive peritoneal lavage cytology. J Surg Oncol. 2012;105(4):393–9.
23. Songun I, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010;11(5):439–49.
24. Sasako M, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008;359(5):453–62.
25. Hirao M, et al. Long-term outcomes after prophylactic bursectomy in patients with resectable gastric cancer: Final analysis of a multicenter randomized controlled trial. Surgery. 2015; 157(6):1099–105.
26. Fujita J, et al. Survival benefit of bursectomy in patients with resectable gastric cancer: interim analysis results of a randomized controlled trial. Gastric Cancer. 2012;15(1):42–8.
27. Kim HI, et al. Standardization of D2 lymphadenectomy and surgical quality control (KLASS-02-QC): a prospective, observational, multicenter study [NCT01283893]. BMC Cancer. 2014;14:209.
28. Fujitani K, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016;17(3):309–318.
29. Bonenkamp JJ, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet. 1995;345(8952):745–8.
30. Cuschieri A, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet. 1996;347(9007):995–9.
31. Cuschieri A, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer. 1999;79(9-10):1522–30.
32. Degiuli M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol. 2004;30(3):303–8.
33. Paoletti X, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA. 2010;303(17):1729–37.
34. Noh SH, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15(12):1389–96.
35. Lee J, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol. 2012;30(3):268–73.
36. Park SH et al. Phase III trial to compare adjuvant chemotherapy with capecitabine and cisplatin versus concurrent chemoradiotherapy in gastric cancer: final report of the adjuvant chemoradiotherapy in stomach tumors trial, including survival and subset analyses. J Clin Oncol. 2015;33(28):3130–6.
37. Glimelius B, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol. 1997;8(2):163–8.
38. Bang YJ, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.

Chapter 11
Gastrointestinal Stromal Tumours

Jennifer Racz, Martin Blackstein, and Fayez A. Quereshy

Introduction

Gastrointestinal stromal tumours (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract and represent ~0.2 % of all gastrointestinal neoplasms [1–3]. These tumours are comprised predominantly of spindle cells and result from activating mutations in the KIT (CD117) proto-oncogene or platelet-derived growth factor receptor alpha gene (PDGFRAα) [4, 5]. Immunohistochemical analysis has been instrumental in identifying markers characteristic of GIST, facilitating its differentiation from other mesenchymal neoplasms. Specifically, these markers include CD117 (95 %), DOG1 (96 %), protein kinase C theta (80 %), CD34 (60–70 %), and smooth muscle actin (30–40 %) [6]. Although they can arise in any location throughout the gastrointestinal tract, they are found primarily in the stomach (60 %) and small intestine (30 %) [7–9]. The cell of origin is the interstitial cell of Cajal [10].

Although the incidence and outcome of GISTs continue to evolve with improvements in detection, surgical technique, and the introduction of targeted molecular therapy, GISTs remain relatively rare tumours, with an estimated annual incidence in Western countries of 0.68–1.5 per 100,000 patients [12].

J. Racz, M.D., M.B.A., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: jennifer.racz@gmail.com

M. Blackstein, M.D., Ph.D., F.R.C.P.C., F.A.C.P.
Department of Medicine, University of Toronto, Toronto, ON, Canada
e-mail: mblackstein@mtsinai.on.ca

F.A. Quereshy, M.D., M.B.A., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: fayez.quereshy@uhn.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_11

Presentation[a] [11, 13]	Prognosis [11, 13] 5-year overall survival (OS)
• Localized (69 %)	64 %
• Metastatic (28 %)	30 %

[a]Due to incomplete epidemiological data on clinical staging, the combined incidence of localized and metastatic disease does not equal 100 %

The American Joint Committee on Cancer AJCC 7th edition is the current recommended staging system for GISTs. Prognostically, a positive regional lymph node (which occurs with an estimated incidence of 5 %) carries the same overall survival as M1 disease [13]. As such, the current AJCC guidelines place lymph node-positive disease as Stage IV.

Management

Primary Resectable GIST

Clinical scenario	Work-up	Management	Follow-up
Gastric tumours < 3 cm	• History and physical exam • Imaging: – CT abdomen and pelvis (gastric protocol) – Upper GI endoscopy (EGD) – Consider EUS and ultrasound-guided biopsy in selected cases (see indications below) • Multidisciplinary consultation	• Management remains controversial for incidental, asymptomatic submucosal gastric masses • In the absence of high-risk EUS features (irregular extra-luminal border, heterogeneous echo pattern, presence of cystic spaces and echogenic foci), close endoscopic and radiographic surveillance is reasonable [14] • Neoplasms that increase in size or become symptomatic should be resected (surgical resection with negative histological margins)	• History and physical exam every 3–6 months • CT abdomen/pelvis (gastric protocol) every 3–6 months for 1–5 years, then annually thereafter. If the mass remains stable over this re-evaluation period, the interval between serial cross-sectional imaging should be increased

(continued)

(continued)

Clinical scenario	Work-up	Management	Follow-up
Localized, resectable tumours > 3 cm	• History and physical exam • Imaging: – CT chest/abdomen/pelvis – MRI scan (rectal neoplasms) – Endoscopy for gastric, duodenal, and rectal locations – Consider EUS and ultrasound-guided biopsy as appropriate • Consider endoscopic or percutaneous biopsy (see indications below) • Multidisciplinary consultation	• Surgical resection with negative histological margins [2, 15, 16] • Routine regional lymphadenectomy is ***NOT*** required • Adjuvant imatinib should be given to intermediate and high-risk patients following R0/R1 resection for 3 years [17–21]	• History and physical exam every 3–6 months • CT chest yearly for 5 years • CT abdomen/pelvis: – Every 3–6 months for 5 years [2, 14] – For low-risk tumours, every 6 months for 5 years [22] – Annually after 5 years

EGD esophagogastroduodenoscopy, *EUS* endoscopic ultrasound

Special Notes

- Biopsy of suspected, resectable GISTs is recommended if:
  - The diagnosis is not clear;
  - Preoperative treatment with imatinib is being considered; and/or
  - Enrollment into a clinical trial is planned.
- Biopsy of GISTs may cause tumour hemorrhage. There is a theoretical but unproven risk of tumour dissemination. Endoscopic ultrasound-guided biopsy is preferred over percutaneous sampling [14], if it can be done expeditiously and effectively.
- Response to imatinib is usually assessed using CT imaging, and is based on a combination of change in size, density, and vascularity [23, 24].
- Laparoscopic resection may be considered provided that oncologic principles and preservation of the tumour pseudocapsule are ensured. Expertise in advanced laparoscopic technique is required.
- Several validated tools utilizing tumour size, mitotic rate, and tumour location have been developed to predict the recurrence risk following surgical resection of primary GISTs [7, 25–28]. Currently, expert opinion holds that mutation status should be determined for all GISTs [29].
- Surgical considerations:
  - No role for regional lymphadenectomy
  - Goal is to achieve negative histological margins
  - *En bloc* resection should be used as needed
  - A laparoscopic approach may be considered in certain circumstances
  - Careful attention must be paid to the integrity of the tumour capsule (tumour rupture may result in disseminated disease)

Locally Advanced/Borderline Resectable/Functionally Unresectable GIST

Work-up	Management	Follow-up
• History and physical exam • Imaging: – CT chest/abdomen/pelvis – MRI scan (rectal neoplasms) – Consider endoscopy – Consider EUS as appropriate • Consider endoscopic or percutaneous biopsy (see indications below) • Consider FDG-PET CT scan and/or DCE-US for borderline resectable cases with early re-evaluation (2–4 weeks after initiation of targeted treatment) [14] • Multidisciplinary consultation	• Neoadjuvant imatinib at a starting dose of 400 mg/day • Early re-evaluation with cross-sectional imaging to assess tumour response to targeted therapy (within 3 months of initiating therapy) • **Responders:** – Imatinib should be continued until maximal tumour response is achieved [30]. However, if the goal of tumour downsizing is achieved (as in the case of borderline resectable disease), it may not be necessary to await maximal tumour response[a] – Surgical resection with negative histological margins following neoadjuvant imatinib is associated with a 12-month overall and progression-free survival of 95 % and 80 %, respectively [33] – *En bloc* resection of adjacent viscera may be considered in order to achieve negative histological margins [2, 15–34] – Routine regional lymphadenectomy is ***NOT*** required • **Non-responders:** – Consider escalating the dose of imatinib to 800 mg/day (as tolerated) or a change to sunitinib [14, 35]; this should also be considered for patients with Exon 9 mutations – Consider surgical resection with negative histological margins ± *en bloc* resection of adjacent viscera if the tumour remains resectable – In patients with tumour progression (following upfront targeted therapy) resulting in unresectable GIST, management is based on the algorithm described for unresectable/recurrent/metastatic disease (see below)	• Close radiographic surveillance every 3 months is necessary, as some patients may become unresectable [9, 10] • Imatinib should be resumed following surgery as soon as oral medications are tolerated, regardless of final surgical margins to minimize the risk of recurrence

FDG-PET 18F-fluorodeoxyglucose-positron emission tomography, *DCE-US* dynamic contrast-enhanced ultrasound

[a]Note: Several more recent studies, however, have demonstrated a negative impact of prolonged neoadjuvant therapy and thus some authors would suggest that neoadjuvant treatment should not exceed 10–12 months; it is thought that this may be related to the development of chemoresistance or the development of new mutations secondary to prolonged therapy [31, 32]

Special Notes

- Functionally unresectable disease is defined as:
  - Localized, non-metastatic GIST at initial presentation;
  - Upfront resection is associated with significant morbidity;
  - Upfront resection is associated with significant long-term functional impairment and/or loss of organ function (i.e. an abdominoperineal resection for a rectal GIST) [2]; and/or
  - Upfront surgery would not yield an R0 resection [22].
- Imatinib mesylate should be initiated at a dose of 400 mg/day [14, 36–38]. Neoadjuvant imatinib has been associated with higher rates of complete resection [31], improved organ preservation [39], and favourable OS and PFS [40] in several case series.
- In patients with advanced GISTs, approximately 90 % of patients respond to imatinib when their tumours have a *KIT* **exon 11** mutation; approximately 50 % of patients respond when their tumours harbor a *KIT* **exon 9** mutation, and the likelihood of response improves with the use of 800 mg/day rather than the standard 400 mg/day dose (based upon tolerance and side effect profile) [14].
- Most mutations in the PDGFRAα gene are associated with a response to imatinib, with the notable exception of D842V [14].
- In the absence of *KIT* and *PDGFRA*α mutations, advanced GISTs have a 0–45 % likelihood of responding to imatinib [14].
- Given the multidisciplinary management of patients with locally advanced/borderline resectable/functionally unresectable GIST, referral to a high-volume surgical oncology center is recommended.

Unresectable, Recurrent, or Metastatic

Work-up	Management	Follow-up (F/U)
• History and physical exam • Imaging: – CT chest/ abdomen/pelvis – MRI scan (rectal neoplasms) – Consider FDG-PET CT scan (may play a role in assessing tumour response to systemic therapy, pre-treatment scan required) – Consider endoscopy – Consider EUS (as appropriate) • Consider endoscopic or percutaneous biopsy (see indications below) • Multidisciplinary consultation	• Imatinib mesylate at a starting dose of 400 mg/day (a starting dose of 800 mg/day should be considered in patients with exon 9 mutations) [14, 22] – The imatinib dose should be escalated when there is evidence of tumour progression to 800 mg/day (as tolerated) [2, 14] – In patients with imatinib resistance (or drug intolerance), consider sunitinib as second-line treatment – In patients with resistance to both imatinib and sunitinib, consideration may be given to third-line tyrosine-kinase inhibitors such as sorafenib, dasatinib, nilotinib, and/or regorafenib [41]. Consider enrollment to available clinical trials as appropriate. • Close radiographic surveillance with CT scans every 3 months should be performed to assess tumour response [2, 14] • Surgery is largely reserved for symptom palliation and may be considered in the context of focally progressive disease refractory to systemic treatment or following a favourable response to systemic treatment[a] • Radiation therapy may be considered for symptomatic bone metastases [14] • Ablative therapies may be considered in localized, solid organ metastases [14] • Embolization may be effective in controlling hemorrhage	• History and physical exam every 3–6 months • CT chest—yearly for 5 years • CT abdomen/pelvis—the first CT scan following the initiation of imatinib should be at 3 months (or sooner based on clinical indication) [14], then every 3 months for 5 years [2, 14] • The interval between consecutive CT scans may be increased based on disease stability [22]

FDG-PET 18F-fluorodeoxyglucose-positron emission tomography

[a]Note: Attempted resection in patients with generalized, progressive disease on imatinib a associated with a 12-month overall and progression-free survival of 0 % [33]

Landmark Trials

Topic	Study	Methods	Results
c-KIT mutation	Hiroti et al. [4]	• Pathological DNA sequencing in GIST specimens	• Gain-of-function mutation in KIT identified in GISTs
Imatinib treatment	Van Oosterom et al. [42]	• Phase I clinical trial • *N* = 40 • Metastatic GIST	• Activity demonstrated with imatinib in GISTs with: – 32/36 (89 %) patients demonstrating inhibition of tumour growth – 19/36 (53 %) patients with partial response (>20 % tumour regression) – 24/27 (89 %) patients with symptomatic improvement
	Demetri et al. [43]	• Phase II Multicentre RCT • *N* = 147 • 400 mg/day imatinib vs. 600 mg/day	• Partial response (PR) to treatment was observed in 53.7 % of patients • Stable disease (SD) in 27.9 % • Early resistance with progressive disease (PD) in 13.6 % • No difference was observed between the two doses
	Heinrich et al. [44]	• Phase II RCT • *N* = 127 • Response to imatinib in metastatic GIST was correlated to exon mutation status within the KIT gene	• Patients with exon 11 and 9 mutations had 83.5 % and 47.8 % response rate, respectively • Patients without a detectable KIT or PDGFRAα mutation did not demonstrate a response to treatment
	Verweij et al. [45]	• Phase III RCT • *N* = 946 • 400 mg/day imatinib vs. 800 mg/day	• No difference in response or overall survival (OS) in the two groups • In short-term follow-up, there was an increase in PFS in the 800 mg/day group (54 % vs. 50 %) • Subgroup analysis showed improved PR in the exon 9 mutation patients with 800 mg/day
	Joensuu et al. [21]	• Phase III RCT • *N* = 400 • 12 vs. 36 months of adjuvant Imatinib (400 mg/day) in patients with high risk of recurrence	• With a median follow-up of 54 months, RFS was improved in the 36-month group relative to the 12-month group (5-year RFS 65.6 % vs. 47.9 %, respectively), as was OS (5-year OS of 92.0 % vs. 81.7 %, respectively)

(continued)

(continued)

Topic	Study	Methods	Results
Sunitinib treatment	Demetri et al. [35]	• Phase III RCT • *N*=312 (imatinib resistant) • Sunitinib vs. placebo	• Progression-free survival (PFS) was 24.1 weeks for sunitinib versus 6 weeks in the placebo arm
Regorafenib treatment	George et al. [46]	• Phase II Multicentre Trial • *N*=34 • Results of regorafenib treatment in patients with advanced GISTs after failure of at least imatinib and sunitinib	• Partial response to treatment was observed in 11.8 % of patients • Stable disease was observed in 64.7 % of patients for ≥16 weeks • Median PFS was 10 months
	Demetri et al. [41]	• Phase III Multicentre RCT • *N*=199 • Best supportive care+regorafenib (160 mg/day) vs. best supportive care+placebo in patients with metastatic or unresectable GIST with failure of at least imatinib and sunitinib	• Improved progression-free survival (PFS) in regorafenib group (4.8 vs. 0.9 months) • No apparent overall survival benefit (may be explained by crossover design)
Surgery	DeMatteo et al. [15]	• Retrospective review • *N*=200 • Results of surgical resection in localized and metastatic disease (pre-imatinib era)	• Initial presentation: – Localized disease (46 %) – Metastatic disease (47 %) – Isolated recurrence (7 %) • 5-year survival following complete resection (R0/R1): 54 % • Survival was largely predicted by tumour size
	Dematteo et al. [17]	• Phase III Multicentre RCT • *N*=713 • Adjuvant imatinib for 1 year after R0/R1 resection (tumours moderate to high risk, >3 cm)	• Improved recurrence-free survival (RFS) for adjuvant imatinib compared to resection alone (98 % vs. 83 % at 1 year) • No statistically significant difference in OS
	Mussi et al. [30]	• Retrospective review • *N*=80 • Surgery for metastatic GIST after best clinical response vs. after focal progression	• 2-year PFS in the best clinical response group (64.4 % vs. 9.7 %) • 5-year DSS was 82.9 % vs. 67.6 % in favour of the best clinical response group

OS overall survival, *RFS* recurrence-free survival, *PFS* progression-free survival, *DSS* disease-specific survival, *PR* partial response

Referring to Medical Oncology

- All patients with histologically confirmed GISTs, other than those with very low to low-risk features, should be referred to medical oncology to (1) evaluate the risk of tumour recurrence; and (2) to establish the role of targeted therapy with a tyrosine-kinase inhibitor. If any doubt exists regarding patient risk stratification, referral to medical oncology is warranted.

Referring to Radiation Oncology

- Patients with symptomatic bone metastases not responsive to targeted therapy should be referred to radiation oncology for consideration of palliative therapy.

Referring to Multidisciplinary Cancer Conference

- All patients with a diagnosis of GIST should be discussed to confirm pathologic diagnosis, determine the indications for mutational analysis, and evaluate the indications for adjuvant or neoadjuvant targeted therapy.
- Patients started on neoadjuvant-targeted therapy or who experience limited progression after responding to targeted therapy should be discussed again at Multidisciplinary Cancer Conference (MCC) to re-evaluate the sequencing of multimodality treatment.

Toronto Pearls

- The multidisciplinary management of GISTs is the cornerstone of evidence-based treatment.
- Neoadjuvant imatinib is ***NOT*** associated with prohibitive risk of bleeding. In fact, surgical experience is that GISTs become less vascular and less friable, and therefore less prone to intraoperative rupture.
- Mutational analysis is part of a complete assessment of GIST.

References

1. Connolly E, Gaffney E, Reynolds J. Gastrointestinal stromal tumors. Br J Surg. 2003;90: 1178–86.
2. Blackstein ME, Blay JY, Corless C, et al. Gastrointestinal stromal tumours: consensus statement on diagnosis and treatment. Can J Gastroenterol. 2006;20:157–63.

3. Kitamura Y, Hirota S, Nishida T. Gastrointestinal stromal tumors (GIST): a model for molecule based diagnosis and treatment of solid tumors. Cancer Sci. 2003;94:315–20.
4. Hirota S, Isozaki K, Moriyama Y, et al. Gain of function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998;279:577–80.
5. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003;299:708–10.
6. Blay JY, von Mehren M, Blackstein ME. Perspective on updated treatment guidelines for patients with gastrointestinal stromal tumors. Cancer. 2010;116:5126–37.
7. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol. 2006;23:70–83.
8. Miettinen M, Sarlomo-Rikala M, Lasota J. Gastrointestinal stromal tumours. Ann Chir Gynaecol. 1998;87:278–81.
9. Hasegawa T, Matsuno Y, Shimoda T, Hirohashi S. Gastrointestinal stromal tumor: Consistent CD117 immunostaining for diagnosis, and prognostic classification based on tumor size and MIB-1 grade. Hum Pathol. 2002;44:669–76.
10. Kindblom LG, Remotti HE, Aldenborg F, et al. Gastrointestinal pacemaker cell tumor (GIPACT): gastrointestinal stromal tumors show phenotypic characteristics of the interstitial cells of Cajal. Am J Pathol. 1998;152:1259–69.
11. Tran T, Davila JA, El Serag HB. The epidemiology of malignant gastrointestinal stromal tumors: an analysis of 1458 cases from 1992 to 2000. Am J Gastroenterol. 2005;100:162–8.
12. Nilsson B, Bumming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: the incidence, prevalence, clinical course, and prognostication in the pre-imatinib mesylate era – a population-based study in western Sweden. Cancer. 2005;103(4):821–9.
13. Woodall C, Brock G, Fan J, et al. An evaluation of 2537 gastrointestinal stromal tumors for a proposed clinical staging system. Arch Surg. 2009;144(7):670–8.
14. vonMehren M, Randal RL, et al. National Comprehensive Cancer Network (NCCN) Clinical practice guidelines in oncology: soft tissue sarcoma. Version 2.2014.
15. DeMatteo RP, Lewis JJ, et al. Two hundred gastrointestinal stromal tumours: recurrence patterns and prognostic factors for survival. Ann Surg. 2000;231:51–8.
16. Ng EH, Pollock RE, Munsell MF, et al. Prognostic factors influencing survival in gastrointestinal leiomyosarcomas. Implications for surgical management and staging. Ann Surg. 1992;215:68–77.
17. DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localized, primary gastrointestinal stromal tumour: a randomized, double blind, placebo-controlled trial. Lancet. 2009;373:1097–104.
18. Gold JS, DeMatteo RP. Combined surgical and molecular therapy: the gastrointestinal stromal tumor model. Ann Surg. 2006;244:176–84.
19. DeMatteo RP, Antonescu CR, Chadaram V, et al. Adjuvant imatinib mesylate in patients with primary high risk gastrointestinal stromal tumor (GIST) following complete resection: Safety results from the U.S. Intergroup Phase II trial ACOSOG Z9000. 2005 ASCO Annual Meeting Proceedings. J Clin Oncol. 2005;23:16S (abstr 9009).
20. Nilsson B, Sjölund K, Kindblom LG, et al. Adjuvant imatinib treatment improves recurrence-free survival in patients with high-risk gastrointestinal stromal tumours (GIST). Br J Cancer. 2007;96(11):1656–8.
21. Joensuu H, Eriksson M, Hatrmann J, et al. Twelve versus 36 months of adjuvant imatinib (IM) as treatment of operable GIST with a high risk of recurrence: Final results of a randomized trial (SSGXVIII/AIO) J Clin Oncol. 2001;29(Suppl) Abstr LBA1.
22. Casali PG, Blay JY. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010;21(Suppl):v98–102.
23. Choi H, Charnsangavej C, de Castro FS, et al. CT evaluation of the response of gastrointestinal stromal tumors after imatinib mesylate treatment: a quantitative analysis correlated with FDG PET findings. Am J Roentgenol. 2004;183:1619–28.
24. Choi H. Response evaluation of gastrointestinal stromal tumours. Oncologist. 2008;13 Suppl 2:4–7.

25. Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Hum Pathol. 2002;33(5):459–65.
26. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008;39:1411–9.
27. Gold JS, Gonen M, Gutierrez A, et al. Development and validation of a prognostic nomogram for recurrence-free survival after complete surgical resection of localized primary gastrointestinal stromal tumour: a retrospective analysis. Lancet Oncol. 2009;10:1045–52.
28. Joensuu H, Vehtari A, Riihimaki J, et al. Risk of recurrence of gastrointestinal stromal tumour after surgery: an analysis of pooled population-based cohorts. Lancet Oncol. 2012;13:265–74.
29. Lasota J, Miettinen M. Clinical significance of oncogenic KIT and PDGFRA mutations in gastrointestinal stromal tumours. Histopathology. 2008;53:245–66.
30. Mussi C, Ronelllenfitsch U, Jakob J, et al. Post-imatinib surgery in advanced/metastatic GIST: is it worthwhile in all patients? Ann Oncol. 2010;21:403–8.
31. Andtbacka RH, Ng CS, Scaife CL, et al. Surgical resection of gastrointestinal stromal tumors after treatment with Imatinib. Ann Surg Oncol. 2007;14(1):14–24.
32. Bednarski BK, Araujo DM, Yi M, et al. Analysis of prognostic factors impacting oncologic outcomes after neoadjuvant tyrosine kinase inhibitor therapy for gastrointestinal stromal tumors. Ann Surg Oncol. 2014;21(8):2499–505.
33. Raut CP, Posner M, Desai J, et al. Surgical management of advanced gastrointestinal stromal tumors after treatment with targeted systemic therapy using kinase inhibitors. J Clin Oncol. 2006;24(15):2325–31.
34. Crosby JA, Catton CN, Davis A, et al. Malignant gastrointestinal stromal tumors of the small intestine: a review of 50 cases from a prospective database. Ann Surg Oncol. 2001;8:50–9.
35. Demetri GD, van Oosteron AT, Garrett CR, et al. Efficacy and safety of sunitinib in patients with advanced gastrointestinal stromal tumour after failure of imatinib: a randomized control trial. Lancet. 2006;368:1329–38.
36. Bauer S, Hartmann JT, Lang H, et al. Imatinib may enable complete resection in previously unresectable or metastatic GIST. Proc Am Soc Clin Oncol. 2004;23:819 (Abstr 9023).
37. Eisenberg BL, Harris J, Blanke CD, et al. Phase II trial of neoadjuvant/adjuvant Imatinib mesylate (IM) for advanced primary and metastatic/recurrent operable gastrointestinal stromal tumor (GIST): early results of RTOG 0132/ACRIN 6665. J Surg Oncol. 2009;99:42–7.
38. McAuliffe JC, Hunt KK, Lazar AJ, et al. A randomized, phase II study of preoperative plus postoperative imatinib in GIST: evidence of rapid radiographic response and temporal induction of tumor cell apoptosis. Ann Surg Oncol. 2009;16:910–9.
39. Sjölund K, Andersson A, Nilsson E, et al. Downsizing treatment with tyrosine kinase inhibitors in patients with advanced gastrointestinal stromal tumors improves resectability. World J Surg. 2010;34(9):2090–7.
40. Blesius A, Cassier PA, Bertucci F, et al. Neoadjuvant imatinib in patients with locally advanced non-metastatic GIST in the prospective BFR14 trial. BMC Cancer. 2011;11:72.
41. Demetri GD, Reichardt P, Kang YK, et al. Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicenter, randomized, placebo-controlled, phase 3 trial. Lancet. 2013;381:295–302.
42. Van Oosterom AT, Judson I, Verweij J, et al. Safety and efficacy of imatinib (ST1571) in metastatic gastrointestinal stromal tumours: a phase I study. Lancet. 2001;358:121–1423.
43. Demetri GD, vonMehren M, von Mehren M, et al. Efficacy and safety of imatinib mesylate in advanced gastrointestinal stromal tumors. NEJM. 2002;347:472–80.
44. Heinrich MC, Corless CL, Demetri GD, et al. Kinase mutations and imatinib response in patients with metastatic gastrointestinal stromal tumor. J Clin Oncol. 2003;21:4342–9.
45. Verweij J, Casali PG, Zalcberg J, et al. Progression-free survival in gastrointestinal stromal tumours with high-dose imatinib: randomized trial. Lancet. 2004;364:1127–34.
46. George S, Wang Q, Heinrich MC, et al. Efficacy and safety of regorafenib in patients with metastatic and/or unresectable GI stromal tumor after failure of Imatinib and sunitinib: a multicenter phase II trial. J Clin Oncol. 2012;30(19):2401.

Chapter 12
Hepatocellular Carcinoma

Gonzalo Sapisochin, Paul D. Greig, Shiva Jayaraman, Peter T.W. Kim, Calvin H.L. Law, and Alice C. Wei

Introduction

Hepatocellular carcinoma (HCC) is the 5th most common cancer in the world and 18th most common cancer in Canada. The incidence of HCC is increasing partially due to the increase in patients with hepatitis C and nonalcoholic steatohepatitis (NASH). In 2013, there were 2040 new cases and 1020 deaths from HCC Canada-wide [1]. The management of HCC depends on the stage of the tumor and the underlying liver function.

G. Sapisochin, M.D. (✉)
Fellow, Hepatopancreatobiliary Surgery, University of Toronto, Toronto, ON, Canada
e-mail: sapisochin@me.com

P.D. Greig, M.D., F.R.C.S.C. • S. Jayaraman, M.D., M.E.Sc., F.R.C.S.C., F.A.C.S.
C.H.L. Law, M.D., M.P.H., F.R.C.S.C. • A.C. Wei, M.D., M.Sc., F.R.C.S.C., F.A.C.S.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: paul.greig@uhn.ca; jayars@stjoe.on.ca; calvin.law@sunnybrook.ca; alice.wei@uhn.ca

P.T.W. Kim, M.D., F.R.C.S.C., F.A.C.S.
Baylor University Medical Center, Annette C. and Harold C. Simmons Transplant Institute, Texas A&M Health Science Center, College of Medicine, Dallas, TX, USA
e-mail: Peter.Kim@baylorhealth.edu

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_12

Presentation	Prognosis [2] 5-Year overall survival (OS)
• Solitary tumor, no vascular involvement (resection)	60–70 %
• Multiple tumors, none > 5 cm	35–40 %
• Lymph node or major vascular involvement	15 %
• Distant metastatic disease	0 %

Disease-free survival is significantly less than overall survival because of the high incidence of recurrence or "de novo" tumors due to the underlying cirrhotic tissue, which is the main risk factor for developing HCC. Even for resectable solitary tumors with no vascular invasion, the 5-year recurrence rate is around 70 %.

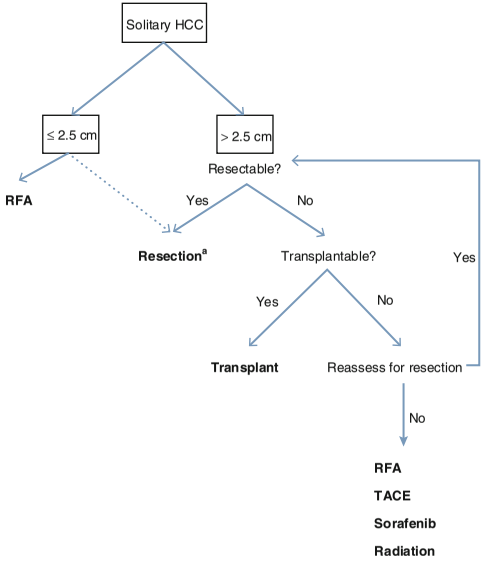
Staging Systems [3]

Clinical (preoperative)	• **Barcelona Clinic for Liver Cancer (BCLC)** • Okuda • International HPB Association (IHPBA) • Cancer of the Liver Italian Program Score (CLIP) • American Study of Liver Tumor Group • Chinese University Prognostic Index (CUPI)
Pathological staging system (postoperative)	• **American Joint Committee on Cancer (AJCC) 7th Ed** • Japanese Integrated Score (JIP) • Tokyo Score
Transplant staging system	• **Milan Criteria** (for priority on the wait list) • UNOS (United Network of Organ Sharing) TNM • Extended Toronto Criteria

Special Notes

- Staging of HCC is complex: both the extent of the tumor and the underlying liver function have to be considered. The most commonly used clinical staging system worldwide is the BCLC.
- The most commonly used pathological staging system is the AJCC.
- For transplantation, the Milan Criteria are the most common staging system used to allocate exception points for tumor priority on the waiting list. Other staging systems are center-specific, but not widely used. The criteria used in Ontario appear in section "Liver Transplantation."

Management of Solitary HCC

Work-up	Treatment	Follow-up
If < 1 cm: • Difficult to fully characterize lesions <1 cm • Recommend 3-month follow-up **If > 1 cm:** • Labs: – AFP – Hepatitis panel – Bilirubin, transaminases, ALP, PT or INR, TB • Imaging: – CT chest, abdo, pelvis – Liver MRI or tri-phasic CT • Biopsy in case of indeterminate lesion both at CT and MRI		• Every 3–6 months for the first 5 years: – AFP – CT chest/abdo • Treat recurrences accordingly • After 5 years, return to routine surveillance for HCC in high-risk patients (q6 monthly US + AFP)

AFP α-feto protein, *RFA* radiofrequency ablation, *TACE* transarterial chemoembolization, *US* ultrasound
[a]Consider liver resection depending on liver function and tumor location

Special Notes

- HCC diagnosis is based on dynamic imaging techniques showing contrast enhancement on the arterial phase and "washout" in the venous phase.
- Considerations for resection:
  - Cirrhotic patient must be Child's A
  - To reduce the risk of postoperative liver failure, the target volume of the future liver remnant (FLR) should be >25–30 % in non-cirrhotic livers and >40 % in cirrhotic livers. If FLR is predicted to be less, portal vein embolization can be performed to induce regenerative hypertrophy and increase the volume of FLR. The radiological response to portal vein embolization may give a good assessment of the liver's ability to withstand a resection.
  - Wide margins, 2 cm better than 1 cm [4]. Anatomic resections (segment-based) are preferred to non-anatomic resections, even though in cirrhotic patients parenchyma sparing is preferred.
- Contraindications for resection:
  - Child B, C cirrhosis
  - Portal hypertension: varices, splenomegaly, thrombocytopenia (platelet count <100/mm [3])
  - Major vascular invasion: main portal venous branches or hepatic veins
  - Extrahepatic disease
- For large (>5 cm) or multiple tumors:
  - Size and multiplicity are not contraindications to surgery.
  - If not a resection candidate, consider transplant evaluation. If the tumor(s) exceed the guidelines for transplantation, consider attempt at downstaging with other treatment options such as ablation, TACE, sorafenib, or radiotherapy.

Management of Multifocal HCC/Advanced Stage

Multifocal	• Liver transplant evaluation (see section "Liver Transplantation") • If not a liver transplant candidate, TACE or consider radiation • The role for resection in multifocal HCC is in highly selected patients
Advanced stage	• In Child B, C cirrhotic patients radiotherapy can be an option • If not candidates for radiotherapy consider best supportive care

TACE transarterial chemoembolization

Liver Transplantation

Criteria	Management
Ontario criteria	• The following tumors are eligible for MELD Exception points: • Milan Criteria or • UCSF Criteria or • Total tumor volume <115 cm^3 [3] and AFP <400 • If otherwise a suitable transplant candidate, list for liver transplant and start locoregional therapy (TACE or RFA or radiation), "bridging therapy" while waiting • Tumors that exceed these criteria may become eligible if successfully "downstaged" and stable for a minimum of 3 months
Toronto extended criteria	• For tumors beyond the Ontario criteria: • If the tumor is well or moderately differentiated and otherwise a suitable transplant candidate, the patient may be eligible for live donor liver transplant: list for liver transplant and consider locoregional therapy if the wait is predicted to exceed 3 months
Liver donation	• For all tumor patients, consider live donor liver transplant if a suitable live donor available

TACE transarterial chemoembolization, *RFA* radiofrequency ablation

Special Notes

- Milan criteria: 1 up to 5 cm or 3 up to 3 cm, with no major vascular invasion, no metastases
- UCFS Criteria: 1 up to 6.5 cm or 3 up to 4.5 cm with total tumor diameter <8 cm with no major vascular invasion, no metastases
- **Toronto Extended Criteria**: no size or number restrictions, well or moderately differentiated tumors on biopsy, no constitutional symptoms, no major vascular invasion, no metastases

Landmark Publications

Radiofrequency Ablation

HCC	Study	Methods	Results
≤2 cm	**Multicenter Italian Study Livraghi et al.** [3]	• Prospective, RFA <2 cm	• Local recurrence: 0.9 % • 5 year survival 68.5 % (resection candidates)
≤3 cm	**Meta-Analysis Mulier et al.** [5]	• Meta-analysis	• Local recurrence 14 %
3–5 cm	**Meta-Analysis Mulier et al.** [5]	• Meta-analysis	• Local recurrence 25 %
≤5 cm	**Chinese RCT Chen et al.** [6]	• RFA vs. resection for <5 cm	• No difference in overall survival or recurrence between RFA and resection
Early HCC	**Meta-Analysis, Zhou Y.** [7]	• Meta-analysis of RFA vs. liver resection	• Liver resection was superior to RFA, specially in HCC >3 cm
Early HCC	**Meta-Analysis, Wang Y.** [8]	• Meta-analysis of RCT and non-RCT of RFA vs. liver resection	• Similar overall survival but higher recurrence rate with RFA

HCC hepatocellular carcinoma, *RCT* randomized controlled trial, *RFA* radiofrequency ablation

Transarterial Chemoembolization (TACE)

- Doxorubicin mixed with lipiodol (targeting agent) administered via subsegmental hepatic artery followed by embolization
- Doxorubicin delivered by drug-eluting microspheres may have lower toxicity and higher efficacy and be suitable for Child B patients

Clinical scenario	Study	Methods	Results
Unresectable HCC	Barcelona Clinic Study Llovet et al. [9]	• RCT • TACE vs. symptomatic treatment	• TACE improved OS compared with symptomatic treatment • TACE: 1-year OS = 82 % and 2-year OS = 63 % • Control: 1-year OS = 63 % and 2-year OS = 27 %
	Hong Kong Study Lo et al. [10]	• RCT • TACE vs. symptomatic treatment	• TACE improved OS • TACE: 1-year OS = 57 %, 2-year OS = 31 % and 3-year OS = 26 % • Control: 1-year OS = 32 %, 2-year OS = 11 %, and 3-year OS = 3 %

HCC hepatocellular carcinoma, *RCT* randomized controlled trial, *RFA* radiofrequency ablation, *OS* overall survival

Resection

HCC	Study	Methods	Results
>10 cm	Sloan Kettering Study Liau et al. [11]	• Prospective cohort	• Long-term survival similar after resection for select patients with HCC >10 cm vs. <10 cm
Multifocal HCC	University of Toronto Kim et al. [12]	• Retrospective study	• High recurrence rate but long-term survival if aggressive treatment of recurrence.
Small HCC	Mount Sinai, NY and Milan, Italy., 2013 [13]	• Retrospective study	• 5-year overall survival 70 %, 5-year recurrence rate 68 %
Margins 2 cm vs. 1 cm	Chinese Wide Margin Study Shi et al. [14]	• RCT	• Long-term survival better with wide (2 cm) margin than narrow (<1 cm) margin (e.g. 5-year survival 74.9 % vs. 70.9 %)

HCC hepatocellular carcinoma, *RCT* randomized controlled trial

Transplantation

Study	Methods	Results
Milan Criteria Mazzaferro et al. [4]	• Retrospective • *N* = 48 patients	• 4-year survival of 75 %
University of California San Francisco (UCSF) Criteria Yao et al. [15]	• Retrospective • *N* = 70 patients	• 1-year survival (OS) of 90 % • 5-year survival of 75 %
Toronto Criteria Dubay et al. [16]	• Retrospective • *N* = 189 within Milan • *N* = 105 outside Milan	• No difference in survival between within Milan and outside Milan • OS: 72 % (Milan), 70 % (outside Milan) • DFS: 70 % (Milan), 66 % (outside Milan)

OS overall survival, *DFS* disease-free survival

Special Notes

- Milan criteria: 1 up to 5 cm, 3 up to 3 cm, no major vascular invasion, no metastases
- UCSF criteria: 1 up to 6.5 cm or 3 up to 4.5 cm or total up to 8 cm
- Toronto criteria: no size or number restrictions, well or moderately differentiated tumors on biopsy, no constitutional symptoms, no major vascular invasion

Systemic Therapy

Study	Methods	Results
SHARP Trial [17]	• RCT for advanced HCC in Child A cirrhotics • *N* = 299 sorafenib, 303 placebo	• Sorafenib resulted in 3-month longer median survival than the placebo group

RCT randomized controlled trial

Guidelines and Consensus Documents

1. American Association for the Study of Liver Diseases (AASLD) Guidelines [18].
2. European Association for the Study of Liver Guidelines [19].
3. Consensus conference on liver transplantation for HCC [20].

Referring to Medical Oncology

1. Patients who are candidates for TACE (Child A, B, no contraindications for angiography)
2. Patients who are candidates for sorafenib (Child A, advanced HCC)

Referring to Radiation Oncology

1. HCC not amenable to TACE

Referring to Multidisciplinary Cancer Conference

1. All HCC patients are discussed at the Multidisciplinary Cancer Conference (MCC) due to the multidisciplinary nature of their management.

Toronto Pearls

- When considering resection, if there is any doubt about FLR, perform portal vein embolization (PVE).
- Treat solitary lesions less than 2.5 cm with RFA as a definitive therapy and consider liver resection depending on liver function and tumor location.
- For single lesions, RFA is preferable to TACE if it meets the size criteria.
- Extended Toronto Criteria for liver transplant allows patients outside Ontario Criteria to be considered for liver transplant.
- Reconsider resection in patients with single HCC who are not transplant candidates.
- Patients with very large (>10 cm) tumors may be amenable for liver resection.

References

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2013. Toronto: Canadian Cancer Society; 2013.
2. Vauthey JN, Lauwers GY, Esnaola NF, et al. Simplified staging for hepatocellular carcinoma. J Clin Oncol. 2002;20(6):1527–36.
3. Livraghi T, Meloni F, Di Stasi M, et al. Sustained complete response and complications rates after radiofrequency ablation of very early hepatocellular carcinoma in cirrhosis: is resection still the treatment of choice? Hepatology. 2008;47(1):82–9.

4. Mazzaferro V, Regalia E, Doci R, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996;334(11):693–9.
5. Mulier S, Ni Y, Jamart J, et al. Local recurrence after hepatic radiofrequency coagulation: multivariate meta-analysis and review of contributing factors. Ann Surg. 2005;242(2):158–71.
6. Chen MS, Li JQ, Zheng Y, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Ann Surg. 2006;243(3):321–8.
7. Zhou Y, Zhao Y, Li B, et al. Meta-analysis of radiofrequency ablation versus hepatic resection for small hepatocellular carcinoma. BMC Gastroenterol. 2010;10:78.
8. Wang Y, Luo Q, Li Y, Deng S, Wei S, Li X. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials. PLoS One. 2014;9(1):e84484.
9. Llovet JM, Real MI, Montaña X, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. Lancet. 2002;359(9319):1734–9.
10. Lo CM, Ngan H, Tso WK, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. Hepatology. 2002;35(5):1164–71.
11. Liau KH, Ruo L, Shia J, et al. Outcome of partial hepatectomy for large (>10 cm) hepatocellular carcinoma. Cancer. 2005;104(9):1948–55.
12. Kim PT, Jang JH, Atenafu EG, et al. Outcomes after hepatic resection and subsequent multimodal treatment of recurrence for multifocal hepatocellular carcinoma. Br J Surg. 2013;100(11):1516–22.
13. Roayaie S, Obeidat K, Sposito C, et al. Resection of hepatocellular cancer ≤2 cm: results from two Western centers. Hepatology. 2013;57(4):1426–35.
14. Shi M, Guo RP, Lin XJ, et al. Partial hepatectomy with wide versus narrow resection margin for solitary hepatocellular carcinoma: a prospective randomized trial. Ann Surg. 2007;245(1):36–43.
15. Yao FY, Ferrell L, Bass NM, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001;33(6):1394–403.
16. DuBay D, Sandroussi C, Sandhu L, et al. Liver transplantation for advanced hepatocellular carcinoma using poor tumor differentiation on biopsy as an exclusion criterion. Ann Surg. 2011;253(1):166–72.
17. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008;359(4):378–90.
18. Bruix J, Sherman M, American Association for the Study of Liver Diseases. Management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2.
19. European Association For The Study Of The Liver, European Organisation For Research And Treatment Of Cancer. EASL-EORTC clinical practice guidelines: management of hepatocellular carcinoma. J Hepatol. 2012;56(4):908–43.
20. Clavien PA, Lesurtel M, Bossuyt PM, et al.; OLT for HCC Consensus Group. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. Lancet Oncol. 2012;13(1):e11–22.

Chapter 13
Melanoma

Mai-Kim Gervais, Nicole J. Look Hong, David R. McCready, Teresa Petrella, and Frances C. Wright

Introduction

In 2014, the Canadian Cancer Society (CCS) reported that melanoma was the seventh most common diagnosed malignancy across Canada. Melanoma represents less than 5 % of all skin cancers, but accounts for the most attributable deaths from skin cancer. In 2014, 6500 new cases and 1050 deaths from melanoma were estimated to have occurred. Between 2001 and 2010, the incidence rates of melanoma increased by 2.2% per year for men and by 2.1 % per year for women [1].

Presentation	Prognosis 5-Year overall survival (OS)
• Localized disease (82–85 %)	90 %
• Regional metastasis (10–13 %)	30–75 %
• Distant metastasis (2–5 %)	15 %

M.-K. Gervais, M.D., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Maikim.gervais@gmail.com

N.J. Look Hong, M.D., M.Sc., F.R.C.S.C. • D.R. McCready, M.S., M.Sc., F.R.C.S.C., F.A.C.S.
F.C. Wright, M.D., M.Ed., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: Nicole.LookHong@sunnybrook.ca; David.McCready@uhn.ca;
frances.wright@sunnybrook.ca

T. Petrella, M.D., M.Sc., F.R.C.P.C.
Department of Medical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Teresa.Petrella@sunnybrook.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_13

The American Joint Committee on Cancer (AJCC) 7th edition is the current recommended melanoma staging system.

Management

Primary Localized Melanoma

Management of melanoma in situ

Work-up	Wide local excision (margins) [2]	Lymph node assessment	Follow-up (F/U) [3–5]
• History and physical exam • No labs • No radiologic studies	• 5 mm clinical margin	• SLNB is not indicated	• Clinically: – Instruct patients on skin examinations (patient education) – Refer to dermatologist – One clinical visit per year

SLNB sentinel lymph node biopsy

Management of melanoma ≤ 1 mm (Breslow depth)

Work-up	Wide local excision (margins) [2]	Lymph node assessment	Follow-up (F/U) [3–5]
• History and physical exam • Clinical assessment of regional lymph nodes and in-transit lesions • No labs • No radiologic studies	• 1 cm clinical margin • Including skin and subcutaneous tissue to the fascia (but not the fascia)	• SLNB is not indicated in most cases (see below)	• Clinically: – Instruct patients on skin examinations (patient education) – Refer to dermatologist – Every 6–12 months for first 3 years, and then annually • No labs • No imaging

SLNB sentinel lymph node biopsy

Special Notes

- When melanoma 0.75–1 mm in depth, discuss the option of SLNB to patients with any of the following features [6–8]:
  - Ulceration (T1b)
  - Mitotic rate ≥ 1/mm^2 (T1b)
  - Microsatellitosis
  - Clark IV/V

- There is a lack of consensus regarding what should be considered a "high-risk feature" in melanomas < 1 mm in depth. Lymphovascular invasion, presence of regression >50 %, vertical growth rate, and absence of tumor infiltrating lymphocytes remain unclear predictors of lymph node positivity. The presence of one of these high-risk criteria in isolation cannot be interpreted as a clear indication for SLNB. Breslow thickness of >0.75 mm alone without any risk factor correlates with increased risk of positive SLN (8.8 %) and SLNB may be justified on the basis of tumor depth only [9].
- Mitotic rate is the most important prognostic factor after tumor thickness for stage I and II cutaneous melanoma and has a greater independent prognostic significance than tumor ulceration [10, 11].
- There is limited evidence to inform follow-up frequency and imaging.
- For subungual melanomas, the appropriate surgical management is a functional amputation (proximal to closest joint or ray amputation).

Management of melanoma 1–4 mm (Breslow depth)

Work-up	Wide local excision (margins) [2]	Lymph node assessment [2]	Follow-up (F/U) [4, 5]
• History and physical exam • Clinical assessment of regional lymph nodes and in-transit lesions • No labs • No standard radiologic studies • Further imaging only if clinically indicated	• 1–2 mm melanoma: – 1–2 cm clinical margin • 2–4 mm melanoma: – 2 cm clinical margin • Margins may be modified to accommodate functional or anatomic considerations • Consultation to plastic surgery if primary closure is compromised (i.e., lower arm/lower leg/high on the back)	• Discuss and offer SLNB	• Clinically: – Stage I: Every 6–12 months for 3 years and then annually – Stage II: Every 6 months for first 2 years, then annually – Stages III–IV: Every 3–6 months for first 3 years, then every 6–12 months for 2 years, and then annually – Patient education – Refer to dermatologist • No labs • No imaging

SLNB sentinel lymph node biopsy

Special Notes

- The updated available Level I evidence is insufficient to determine optimal excision margins for melanoma, including all Breslow thickness [12, 13]. Recommendations are based on consensus/guidelines.
- Excision of the fascia is not necessary except in the case of documented clinical or radiologic invasion. Margins are determined from the edge of the lesion or the incision excision/biopsy scar. Adequate margins are assessed clinically. Reexcision is recommended with involved margins.

Management of melanoma ≥ 4 mm (Breslow depth)

Work-up	Wide local excision (margins) [2]	Lymph node assessment	Follow-up (F/U) [4, 5]
• History and physical exam • Clinical assessment of regional lymph nodes and in-transit lesions • No labs • Imaging: – CT or MRI of brain[a] + – CT chest, abdomen and pelvis – OR PET/CT ± MRI brain[a]	• 2 cm clinical margin • Margins may be modified to accommodate functional or anatomic considerations • Consultation to plastic surgery if necessary if primary closure is compromised	• Discuss and offer SLNB	• Clinically: – Stage II: Every 3–6 months for first 2 years, then every 6–12 months for 2 years, and then annually – Stages III–IV: Every 3–6 months for first 3 years, then every 6–12 months for 2 years, and then annually • No labs • No imaging

SLNB sentinel lymph node biopsy
[a]Depending on institutional preference or availability

Special Notes

- There is very limited data with no evidence about improved outcomes with standard metastatic work-up. This is left to the discretion of individual physicians.
- Controversy exists regarding clinical value of sentinel lymph node assessment for thick melanoma. T4 melanomas have higher risk of systemic metastases at initial diagnosis, and patients might not benefit from lymphadenectomy in terms of survival. However, for thick melanoma without distant metastases, SLNB remains useful for staging, prognostication, and locoregional control [14]. Thick melanomas have a 42 % risk of node positivity at 10 years and SLN status still represents the most important survival prognostic factor [15, 16]. Lymphadenectomy confers a 10-year disease-free survival benefit mostly for intermediate thickness melanoma. Among patients with intermediate thickness with nodal metastases, there is a benefit in 10-year melanoma-specific survival in the biopsy group (62.1 %) compared to the observation group (41.5 %) [15, 16].
- There is a lack of valid prospective studies of the efficacy of routine follow-up.
- No study has demonstrated an improvement in survival due to routine imaging surveillance.

Regionally Metastatic Melanoma

Clinical scenario	Work-up	Surgical approach [15, 17–19]
SLNB positive [15, 17–19]	• Metastatic work-up with: – CT head or MRI of brain + – CT chest, abdomen, and pelvis – OR PET/CT ± MRI brain	• Completion lymphadenectomy (CLND) is discussed and offered[a] • MSLT-2 trial—accrual completed • Observation + ultrasound monitoring (if patient refuses further surgery or not surgical candidate) • Refer to medical oncology for assessment of adjuvant therapy/clinical trial • Consider consultation to radiation oncology for adjuvant radiation therapy
Clinically positive lymph node	• FNA or lymph node biopsy • Imaging: – CT or MRI of brain + – CT chest, abdomen, and pelvis – OR PET/CT ± MRI brain	• Completion lymphadenectomy • Refer to medical oncology for assessment of adjuvant therapy/clinical trial • Consider consultation to radiation oncology for adjuvant therapy and/or for unresectable disease • Consideration of neoadjuvant therapy to enable resection
In-transit or satellite lesions [20–22]	• FNA or excisional/incisional biopsy • Imaging: – CT or MRI of brain + – CT chest, abdomen, and pelvis – OR PET/CT ± MRI brain	• Single lesion: – Surgical excision with clear margins + consider SLNB (if it has not been performed previously) – Refer to medical oncology for assessment of adjuvant therapy (interferon-α)/clinical trial • Multiple lesions (no consensus): – Resection if feasible – Isolated limb perfusion/infusion with melphalan ± dactinomycin. Possible improvement in DFS and OS with complete response. Similar overall response (50–85 %) rate between ILI and ILP. Increased toxicity with ILP. – Intralesional therapy with IL-2, interferon-α, or BCG. Phase III trial of intralesional VP10/Rose Bengal ongoing – Topical therapy with imiquimod or diphencyprone cream (DPCP) – T-VEC: viral vaccine talimogene laherparepvec. Objective response in 26 % and complete response in 11 % of cases. Clinical trials [23] – Radiation therapy for unresectable disease – Combination of systemic therapy with intralesional treatment/clinical trials

MSLT-2 multicenter selective lymphadenectomy trial 2 (NCT 00297895), *SLNB* sentinel lymph node biopsy, *FNA* fine-needle aspiration, *CLND* completion lymphadenectomy, *ILI* isolated limb infusion, *ILP* isolated limb perfusion, *BCG* Bacille Calmette-Guérin, *OS* overall survival

[a]No randomized trials have demonstrated the therapeutic value of completion lymph node dissection

Special Notes

- The rate of successful SLNB is 98.1 % with an overall false-negative rate of 12.5 %. In high-volume centers with >50 cases/year, a false-negative rate of 5 % (local recurrence rate 5 %) is achieved [24]. We recommend performing SLNB with preoperative lymphoscintigraphy and using both blue dye and radioactive dye. Approximately 15–20 % of patients with a positive sentinel lymph node will have melanoma metastases identified in completion lymphadenectomy [14, 25]. CLND has not been proven to increase overall survival after positive sentinel node and about 80–85 % of the time, SLN is the only positive node. These patients might be exposed to unnecessary morbidity [26]. MSLT-2 trial aims to define the therapeutic value of CLND versus observation after positive SLN.
- Completion lymphadenectomy in the axilla usually requires levels 1, 2, and 3 dissection with selective transection of pectoralis minor [27]. Some argue that level 3 axillary dissection should be performed only when palpable nodes are present [28, 29].
- In the groin, superficial inguinal lymphadenectomy remains the current standard of treatment with non-palpable positive SLN and absence of abnormal pelvic lymphadenopathy on imaging. Extent of dissection including deep iliac/obturator dissection is controversial. Deep iliac/obturator lymphadenectomy should be completed in the presence of pelvic node involvement on pre-operative imaging (CT scan or PET/CT). Deep iliac/ obturator lymphadenectomy should be considered in the presence of clinically detected superficial inguinal node disease, positive Cloquet's node and multiple positive (>= 3) positive sentinel nodes [30].
- Neoadjuvant therapies in the context of unresectable/borderline resectable regional disease have been studied. Chemotherapy such as temozolomide has been shown to be ineffective in the neoadjuvant setting in a small phase II study with a 15 % response rate, similar to what is seen in the metastatic setting [31]. Neoadjuvant high-dose interferon has shown a response rate of 55 %, but with high toxicity and 50 % recurrence at 18 months [32]. Biochemotherapy combining IL-2, interferon-alpha, and multiagent chemotherapy demonstrated high response rates (40 %) but with substantial toxicity [33]. Vemurafenib improved both DFS and OS in BRAF mutant metastatic melanoma patients. High response rate and low toxicity make vemurafenib an ideal neoadjuvant therapy; however currently no studies have been completed in this patient population [34].

- Intralesional interleukin-2 (IL-2) for the treatment of in-transit melanoma has an overall response rate of 82 %, with complete clinical response in 51–69 % of patients and complete pathologic response rate of 32 % [35]. When complete clinical response is achieved, an increase in 5-year overall survival can be obtained, compared to partial responders (80 % vs. 33 %, respectively) [36, 37]. However, this increase in survival might not necessarily represent a direct effect of intra-tumoral IL-2 and could be biased by selection of cases with less aggressive disease [38]. Unlike systemic IL-2, intralesional IL-2 is well tolerated with much less toxicity.

Rationale for sentinel lymph node biopsy	
Accurate staging • Allows a more rational follow-up strategy	
Prognostic factor • The 5-year overall survival for patients with nodal micrometastases is 67 % and with nodal macrometastases, 43 % [39]	
Better locoregional control • Complication rates of SLNB vs. lymphadenectomy: 4.6 % vs. 23.2 % [17, 40] • By identifying micrometastases (through SLNB), patients are less likely to require radiation to the nodal basin, and thus a lower chance of lymphedema • Lymphedema rate for axillary SLNB vs. complete lymphadenectomy: 1.7 % and 9 %, respectively [17, 41] • Lymphedema rate for groin SLNB vs. complete lymphadenectomy: 1.7 % and 26 %, respectively [17, 41]	
Potential/unclear survival benefit • In SLN-positive patients [16], to date, there is no definite evidence that SLNB followed by lymphadenectomy for positive nodes confers a survival benefit	
Impact in adjuvant therapy • Accurate nodal staging information is important in order to offer patients enrolment in ongoing clinical trials • Small benefit of interferon	
Tumor thickness likelihood of positive SN	
<0.8 mm	<1 %
0.8–1.5 mm	8 %
1.5–4.0 mm	23 %
>4.0 mm	42 %

Distant Metastatic Melanoma

Work-up	Surgical approach [42–45]	Systemic therapy [46]
• Labs: – Serum LDH – CBC, lytes, BUN, Cr, LFTs • Imaging: – CT or MRI of brain – CT chest, abdomen, and pelvis – PET/CT scan if considering surgical intervention	• Metastasectomy—careful consideration of complete resection in: – Pulmonary metastases (survival benefit)—5-year OS of 20 % if complete metastasectomy compared to 4 % if incomplete resection – Symptomatic GI metastases – Symptomatic brain metastases (surgery, stereotactic radiosurgery, or whole-brain radiation) – Symptomatic adrenal metastases – Liver metastases—survival benefit only shown in retrospective studies from ocular melanoma when complete metastasectomy – Subcutaneous metastases – Palliation of symptoms	• Clinical trial whenever available and appropriate • Targeted therapies dependent on mutational status (BRAF, cKIT, MEK, NRAS, GNAQ genes) – V600 BRAF mutation positive (43–50 % of cases): offer clinical trial or BRAF inhibitor – BRAF inhibitor (vemurafenib, dabrafenib): rapid tumor response, but common progression of disease within 6–12 months of treatment. Preferred option for symptomatic or rapidly progressive disease – MEK inhibitor—alone or in combination with BRAF inhibitor/clinical trials. Combined treatment offers a longer PFS – cKIT: featured in acral and mucosal melanoma • Immunotherapy – Ipilimumab: Slow but durable response in 20 % of patients – Systemic IL-2: objective response in 20 % of cases, complete response in 7 % [42]. Significant toxicity. – Anti-PD1: monoclonal antibody against PD-1. Preferred option for stage IV disease – Anti-PDL1—antibody against PD-1 ligand. Clinical trials • Systemic chemotherapy (dacarbazine, temozolomide, carbo/taxol and abraxane): Dacarbazine and temozolomide have a clinical response rate of 15–20 % and a complete response rate of 3–5 % [42]

LFT liver function test, *PET* positron emission tomography, *OS* overall survival, *PFS* progression-free survival

Special Notes

- Most common causes of death with metastatic melanoma are respiratory failure and intracranial metastases. A phase II trial of complete resection for stage IV melanoma (SWOG, S9430 trial) reported a 4-year OS of 31 % with median survival of 21 months [47]. 5-Year survival of 40 % has also been reported for complete metastasectomy when tumor-free margins are obtained [42]. When resection of melanoma metastases ± systemic therapy was compared to systemic medical therapy alone, median survival was 15.8 vs. 6.9 months and surgical treatment conferred a 4-year survival of 20.8 % vs. 7.0 %. Distant disease-free interval of more than 12 months, M1a, and lower number of organ sites of metastases were associated with improved survival [48]. Optimal sequencing of recent systemic therapies with metastasectomy remains unclear.

Landmark Trials

Wide Local Excision: Margins

Melanoma (Breslow thickness)	Study	Methods	Results
• In situ	• No RCTs	–	–
• <1 mm – No specific RCTs	**French Cooperative Surgical Trial** [49]	• $N=337$ (melanoma < 2.1 mm) • Excision margins: 5 cm vs. 2 cm • Median F/U: 16 years	• No difference in OS • LR not reported
	Swedish Cooperative Surgical Trial [50]	• $N=989$ (melanoma 0.8–2.0 mm) • Excision margins: 5 cm vs. 2 cm • Median F/U: 11 years	• No difference in OS • LR: <1 % overall
	WHO Melanoma Program Trial [51]	• $N=612$ (melanoma ≤ 2 mm) • Excision margins: 3–5 cm vs. 1 cm • Median F/U: 15 years	• No difference in OS • No difference in LR
• 1–4 mm – French, Swedish and WHO trials plus:	**Intergroup Melanoma Surgical Trial** [52, 53]	• $N=740$ (melanoma 1.0–4.0 mm) • Excision margins: 4 cm vs. 2 cm • Median F/U: 10 years	• No difference in OS • No difference is LR
	British Cooperative Group Trial [54]	• $N=675$ (melanoma 2.0–4.0 mm) • Excision margins: 3 cm vs. 1 cm • Median F/U: 5 years	• No difference in OS same • Lower LR with 3 cm margins ($p=0.05$)

(continued)

(continued)

Melanoma (Breslow thickness)	Study	Methods	Results
• >4 mm	**British Cooperative Group Trial** [54]	• *N* = 225 (melanoma > 4 mm) • Excision margins: 3 cm vs. 1 cm • Median F/U: 5 years	• No difference in OS

F/U follow-up, *RCT* randomized controlled trials, *WLE* wide local excision, *OS* overall survival, *NS* not significant, *LR* locoregional recurrence, *CLND* completion lymphadenectomy—immediate, *DFS* disease-free survival, *TLND* therapeutic lymphadenectomy—delayed, *SLN* sentinel lymph node

Sentinel Lymph Node Biopsy

Study	Methods	Results
Multicenter Selective Lymphadenectomy Trial (MSLT-1) [15, 16]	• RCT • *N* = 1347 (melanoma 1.2–3.5 mm), 314 with thick melanoma • Groups: WLE + SLNB (with CLND if positive) vs. WLE and observation (with TLND when clinically nodal relapse) • Median F/U: 10 years	• 5-year DFS 78 % vs. 73 % ($p = 0.009$) • 10-year DFS SLNB vs. observation for intermediate thickness: 71.3 % vs. 64.7 % ($p = 0.01$) and for thick melanoma: 50.7 % vs. 40.5 % ($p = 0.03$) • No significant difference in 10-year melanoma-specific survival in intermediate-thickness melanoma (81.4 % in SLNB group vs. 78.3 % in observation group, $p = 0.18$) and in thick melanoma (58.9 % vs. 64.4 %, $p = 0.56$) • Subgroup analysis in positive sentinel node patients: – Better 10-year OS in those who were SLN+ and had CLND vs. those who had TLND (62.1 % vs. 41.5 %, $p = 0.006$) • Node-negative patients have 10-year OS of 85.1 % vs. 62.1 % for those with node-positive disease ($p < 0.001$) • In multivariable analysis, sentinel node status is the strongest predictor of disease recurrence and death from melanoma

(continued)

(continued)

Study	Methods	Results
Multicenter Selective Lymphadenectomy Trial (MSLT-2) NCT00297895	• Phase III multicenter RCT • Groups: Sentinel Lymphadenectomy and Complete Lymph Node Dissection Versus Sentinel Lymphadenectomy Alone in Cutaneous Melanoma Patients With Molecular or Histopathological Evidence of Metastases in the Sentinel Node • Accrual completed in 2014 • Estimated study completion date : 2022	

RCT randomized controlled trial, *WLE* wide local excision, *OS* overall survival, *LR* locoregional recurrence, *NS* not significant, *CLND* completion lymphadenectomy—immediate, *TLND* therapeutic lymphadenectomy—delayed, *SLN* sentinel lymph node, *DFS* disease-free survival

Systemic Therapy

Drug	Study	Methods	Results
Vemurafenib	Chapman PB et al. [55]	• RCT • Vemurafenib (BRAF inhibitor) vs. dacarbazine in previously untreated metastatic melanoma with the BRAF V600E mutation	• At 6 months, OS was 84 % for vemurafenib group vs. 64 % for dacarbazine • Relative reduction 63 % in risk of either death and 74 % in risk of disease progression as compared with dacarbazine • PFS of 5.3 vs. 1.6 months with dacarbazine
Dabrafenib	Hauschild A et al. [56]	• RCT • Dabrafenib (BRAF inhibitor) vs. dacarbazine in previously untreated unresectable stage III or IV BRAF-mutated melanoma	• Median PFS 5.1 months for dabrafenib vs. 2.7 months for dacarbazine (HR 0.30, $p<0.0001$) • Adverse events 53 % dabrafenib group vs. 44 % dacarbazine group
Trametinib	Flaherty KT et al. [57]	• RCT • Trametinib (MEK inhibitor) vs. dacarbazine vs. paclitaxel in previously untreated BRAF-mutated metastatic melanoma	• 6-month OS 81 % trametinib vs. 67 % chemotherapy • Median PFS 4.8 months in trametinib vs. 1.5 months in chemotherapy groups (HR 0.45, $p<0.001$)

(continued)

(continued)

Drug	Study	Methods	Results
Ipilimumab	Robert C et al. [58]	• RCT • Ipilimumab (Anti-CTLA-4) + dacarbazine vs. dacarbazine + placebo in previously untreated metastatic melanoma	• OS significantly longer in Ipi + D vs. D + placebo—11.2 vs. 9.1 months with higher survival rates at: – 1 year (47.3 % vs. 36.3 %) – 2 years (28.5 % vs. 17.9 %) – 3 years (20.8 % vs. 12.2 %)
Interferon-alpha	Kirkwood JM et al., 1996—Eastern Cooperative Oncology Group (EGOG 1684) [59]	• RCT • High-dose IFN alpha-2b vs. observation in stage IIB and III primary or recurrent regional nodal metastases	• 5-year RFS 37 % vs. 26 % • 5-year OS 46 % vs. 37 % • Dose modification in majority of patients due to toxicity
	Kirkwood JM et al., 2000—Eastern Cooperative Oncology Group (EGOG 1690) [60]	• RCT • High-dose IFN-alpha for 1 year vs. low-dose IFN-alpha for 2 years vs. observation in stages IIB and III or recurrent regional nodal metastases	• RFS benefit of IFN alpha is dose dependent (44 % vs. 40 % vs. 35 %) • No significant survival benefit (5-year OS 52 % vs. 53 % vs. 55 %)
	Wheatley K et al. [61]	• Meta-analysis • 12 trials, comparisons of IFN-alpha with controls	• Absolute difference in DFS of 7 % with IFN-alpha • OS benefit is not significant, but absolute survival difference of 3 % with IFN-alpha • The difference in treatment effect is dependent on doses of IFN-alpha. Benefit of IFN-alpha tends to increase with increasing total scheduled dose ($p = 0.05$)
Combined BRAF and MEK inhibitors	Long GV et al. [62]	• RCT • Dabrafenib (BRAF inhibitor) + trametinib (MEK inhibitor) vs. dabrafenib + placebo in previously untreated unresectable stage IIIC or stage IV melanoma with BRAF mutation	• Median PFS 9.3 months in combination group vs 8.8 months in dabrafenib-alone group • Overall response rate: 67 % vs. 51 % • At 6 months, OS 93 % vs. 85 % ($p = 0.02$) • Similar adverse events
	Larkin J et al. [63]	• RCT • Vemurafenib (BRAF inhibitor) + cobimetinib (MEK inhibitor) vs. vemurafenib + placebo in untreated unresectable locally advanced or metastatic BRAF mutation-positive melanoma	• Median PFS 9.9 months in combination group vs. 6.2 months in vemurafenib-alone group • Overall response rate: 68 % vs. 45 % • At 9 months, OS 81 % vs. 73 % ($p = 0.046$) • Higher rate of adverse events Grades 3–4 with combination group

(continued)

(continued)

Drug	Study	Methods	Results
Anti-PD1	Wolchok JD et al. [64]	• Phase 1 trial • Nivolumab (Anti-PD1) + ipilimumab intravenously, combined or sequenced regimens	• Objective response in 40 % and 20 % of cases in combined and sequenced regimens, respectively
	Topalian SL et al. [65]	• Retrospective • *N* = 107 • IV Nivolumab q 2 weeks for up to 96 weeks in advanced melanoma	• Median OS 16.8 months, 1- and 2-year OS 62 % and 43 %, respectively • Median PFS 3.7 months • Objective response rate 31 %
	Hamid O et al. [66]	• Retrospective • *N* = 135 • IV Lambrolizumab q 2–3 weeks in advanced melanoma	• Median PFS > 7 months • Objective response rate 38 %

RCT randomized controlled trial, *PFS* progression-free survival, *OS* overall survival, *D* dacarbazine, *RFS* relapse-free survival, *DFS* disease-free survival, *IFN* interferon

Referring to Medical Oncology (Patients with High-Risk Melanoma)

1. Primary melanoma with Breslow thickness > 4 mm
2. Node-positive melanoma
3. In-transit or satellite lesions
4. Metastatic disease
5. Recurrent disease
6. Unknown primary melanoma

Patients with metastatic melanoma should be referred for clinical trials whenever possible. Metastatic melanoma of the unknown primary site is diagnosed in approximately 2–9 % of all melanoma cases. It is usually diagnosed if metastatic melanoma is confirmed clinically and pathologically, and if no cutaneous, uveal, or mucosal melanoma primary can be found. Data suggests that unknown primary melanoma can be accurately staged using the AJCC staging system, and have equal survival stage per stage [70].

Cancer Care Ontario (CCO) and the Melanoma Disease Site Group recommend that high-dose interferon alpha-2b therapy for 1 year should be discussed with and offered to patients with high-risk melanoma for adjuvant therapy. Pegylated IFN can be used as an alternative to high-dose IFN-alpha [71]. Meta-analyses and randomized controlled trials demonstrated increased recurrence-free survival rate with IFN-alpha (7 % absolute risk reduction at 5 years), but little effect on overall survival (3 % absolute benefit in 5-year OS) [61, 72]. Tumor burden in lymph nodes and ulceration of the primary tumor have been reported as predictors for benefit from adjuvant IFN-alpha [73]. Because the actual overall survival benefit with systemic therapy is relatively small (3 %), patients should be encouraged to participate in available clinical trials.

Referring to Radiation Oncology [74–76]

1. Gross residual disease
2. Extracapsular nodal extension
3. ≥2 cervical, ≥2 axillary, ≥3 inguinal lymph nodes involved
4. Cervical lymph node ≥ 2 cm, axillary and inguinal lymph node ≥ 3 cm
5. Therapeutic lymph node dissection not possible after positive sentinel node
6. Unresectable in-transit/satellite metastases and isolated limb perfusion/infusion is not effective or not possible [22]
7. Metastatic disease—if symptomatic from focal disease; treatment of brain metastases with stereotactic radiosurgery or whole-brain radiation therapy
8. Pure desmoplastic melanoma with narrow margins, locally recurrent or extensive neurotropism [77]

Referring to Multidisciplinary Cancer Conference (MCC)

1. Melanoma with Breslow thickness < 1 mm
2. Bulky nodal disease
3. New metastatic disease
4. In-transit or locoregional recurrence
5. Any consideration of non-standard multimodal therapy
6. Consideration of available clinical trials

Desmoplastic Melanoma

Desmoplastic melanoma (DM) constitutes less than 4 % of all primary cutaneous melanomas and is most commonly located on head and neck. Neurotropism and absence of BRAF mutation are common features of DM. DM is pathologically characterized by spindle-shaped cells with atypical melanocytic proliferation and abundant collagen stroma [78]. Desmoplastic melanoma is classified into pure and mixed subtypes. Pure subtype DM is defined by a predominance of stromal fibrosis with >90 % desmoplasia while mixed DM is characterized by the presence of desmoplasia within 10–90 % of the tumor [79].

DM has favorable survival prognosis compared to conventional melanoma subtypes with a lower risk of distant metastases. However, DM has an increased risk of local recurrence (5-year local recurrence rate of 17 %). Radiation therapy may improve the rate of local recurrence [77]. Recommendation on SLNB is controversial, with overall rate of positive SLN ranging between 0 and 15 %, but should be considered and discussed with patients [77, 79]. DM featuring mixed subtype has a 24.6 % rate of SLN positivity vs. 9 % with pure subtype [79].

Toronto Pearls

- Groin dissection flaps should preserve Scarpa's fascia with the flap.
- Saphenous vein preservation during groin dissection could be considered if micrometastatic nodal disease only.
- Consider IL-2 intra-tumoral injection in the management of multiple in-transit metastases as first-line treatment.
- For patients at high risk for local failure and those who only underwent superficial groin dissection, consider postoperative surveillance with CT of the abdomen/pelvis to identify patients who could develop iliac/obturator node recurrence and be candidates for further salvage surgery.
- Consider radiation therapy for pathologic positive margins from satellitosis or lymphovascular invasion around the primary site.
- If patient declines completion lymphadenectomy after a positive SLNB, perform ultrasound monitoring of the axilla and/or groin every 6 months for 3 years and then yearly to 5 years.
- Level 3 axillary dissection should be completed in the presence of palpable axillary disease. In the presence of positive axillary SLNB, level 1–2 dissection can suffice.

References

1. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2014. Toronto, ON: Canadian Cancer Society; 2014.
2. Wright F, Spithoff K, Easson A, et al. and the Melanoma Disease Site Group. Primary excision margins and sentinel lymph node biopsy in clinically node-negative cutaneous melanoma of the trunk or extremities. Available at http://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/melanoma-ebs/
3. Coit DG, Thompson JA, Andtbacka R, et al. NCCN clinical practice guidelines in oncology (NCCN guidelines_) for melanoma (version 3.2014). Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp
4. British Columbia Cancer Agency. Melanoma follow-up. Available at: http://www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Skin/Melanoma/ManagementPolicies/Follow-up.htm
5. Alberta Cutaneous Tumor Team. Referral and follow-up surveillance of cutaneous melanoma. Available at: http://www.albertahealthservices.ca/hp/if-hpcancer-guide-cu001-followup-surveillance.pdf
6. Han D, Zager JS, Shyr Y, et al. Clinicopathologic predictors of sentinel lymph node metastasis in thin melanoma. J Clin Oncol. 2013;31:4387–93.
7. Kupferman ME, Kubik MW, Bradford CR, et al. The role of sentinel lymph node biopsy for thin cutaneous melanomas of the head and neck. Am J Otolaryngol. 2014;35(2):226–32.
8. Maurichi A, Miceli R, Camerini T, et al. Prediction of survival in patients with thin melanoma: results from a multi-institution study. J Clin Oncol. 2014;32:2479–85.
9. Andtbacka RH, Gershenwald JE. Role of sentinel lymph node biopsy in patients with thin melanoma. J Natl Compr Canc Netw. 2009;7(3):308–17.
10. Thompson JF, Soong SJ, Balch CM, et al. Prognostic significance of mitotic rate in localized primary cutaneous melanoma: an analysis of patients in the multi-institutional American Joint Committee on Cancer Melanoma Staging Database. J Clin Oncol. 2011;29:2199–205.
11. Cordeiro E, Gervais MK, Look Hong N, et al. Sentinel lymph node biopsy in thin melanoma: a systematic review and meta-analysis. SSO Annual meeting Abstract 2015.

12. Lens MB, Nathan P, Bataille V. Excision margins for primary cutaneous melanoma. Updated pooled analysis of randomized controlled trials. Arch Surg. 2007;142:885–91.
13. Sladden MJ, Balch C, Barzilai DA, et al. Surgical excision margins for primary cutaneous melanoma. Cochrane Database Syst Rev. 2009;4:CD004835.
14. Wong SL, Balch CM, Hurley P, et al. Sentinel lymph node biopsy for melanoma: American Society of Clinical Oncology and Surgical Society of Oncology joint clinical practice guideline. J Clin Oncol. 2012;30(23):2912–8.
15. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med. 2006;355(13):1307–17.
16. Morton DL, Thompson JF, Cochran AJ, et al. Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med. 2014;370:599–609.
17. McMasters KM, Noyes RD, Reintgen DS, et al. Lessons learned from the sunbelt melanoma trial. J Surg Oncol. 2004;86:212–23.
18. Pasquali S, Mocellin S, Campana LG, et al. Early (sentinel lymph node biopsy-guided) versus delayed lymphadenectomy in melanoma patients with lymph node metastases. Cancer. 2010;116:1201–9.
19. Wong SL, Morton DL, Thompson JF, et al. Melanoma patients with positive sentinel nodes who did not undergo completion lymphadenectomy: a multi-institutional study. Ann Surg Oncol. 2006;13:809–16.
20. Cornett WR, McCall LM, Petersen RP, et al. Randomized multicenter trial of hyperthermic isolated limb perfusion with melphalan alone compared with melphalan plus tumour necrosis factor: American College of Surgeons Oncology Group Trial Z0020. J Clin Oncol. 2006;24:4196–201.
21. Lens MB, Dawes M. Isolated limb perfusion with melphalan in the treatment of malignant melanoma of the extremities: a systematic review of randomized controlled trials. Lancet Oncol. 2003;4:359–64.
22. Abbott AM, Zager JS. Locoregional therapies in melanoma. Surg Clin N Am. 2014;94: 1003–15.
23. Andtbacka RHI, Collichio FA, Amatruda T, et al. OPTiM: a randomized phase iii trial of talimogene laherparepvec (T-VEC) versus subcutaneous (SC) granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment of unresected stage IIIB/C and IV melanoma. J Clin Oncol. ASCO Annual Meeting Abstract 2013;31 (Suppl):9008.
24. Valsecchi ME, Silbermins D, de Rosa N, et al. Lymphatic mapping and sentinel lymph node biopsy in patients with melanoma: a meta-analysis. J Clin Oncol. 2011;29(11):1479–87.
25. McMasters KM, Reintgen DS, Ross MI, et al. Sentinel lymph node biopsy for melanoma: controversy despite widespread agreement. J Clin Oncol. 2001;19:2851–5.
26. Van derSau PAP, van Akkooi AC, Verhoef C, et al. Completion lymph node dissection after a positive sentinel node: no longer a must? Curr Opin Oncol. 2013;25(2):152–9.
27. Mohan N, Kamdar D, Wright F, et al. The use of the pectoralis major flap elevation approach to Level 3 axillary tumours. Open Access Surg J. 2013.
28. Serpell JW, Carne PWG, Bailey M, et al. Radical lymph node dissection for melanoma. ANZ J Surg. 2003;73:294–9.
29. Meyer T, Merkel S, Gohl J, et al. Lymph node dissection for clinically evident lymph node metastases of malignant melanoma. Eur J Surg Oncol. 2002;28:424–30.
30. Mack LA, McKinnon JG. Controversies in the management of metastatic melanoma to regional lymphatic basins. J Surg Oncol. 2004;86(4):189–99.
31. Shah GD, Gold JS, Wolchok JD, et al. Phase II trial of neoadjuvant temozolomide in resectable melanoma patients. Ann Oncol. 2010;21:1718–22.
32. Moschos SJ, Edington HD, Land SR, et al. Neoadjuvant treatment of regional stage IIIB melanoma with high-dose interferon alfa-2b induces objective tumor regression in association with modulation of tumor infiltrating host cellular immune responses. J Clin Oncol. 2006;24:3164–71.
33. Gibbs P, Anderson C, Pearlman N, et al. A phase II study of neoadjuvant biochemotherapy for stage III melanoma. Cancer. 2002;94:470–6.
34. Young K, Minchom A, Larkin J. BRIM-1, -2 and -3 trials: improved survival with vemurafenib in metastatic melanoma patients with a BRAF(V600E) mutation. Future Oncol. 2012;8:499–507.

35. Hassan S, Petrella TM, Zang T, et al. Pathologic complete response to intralesional Interleukin-2 therapy associated with improved survival in melanoma patients with in-transit disease. Ann Surg Oncol. 2014;22(6):1950–8.
36. Boyd KU, Wehrli BM, Temple CLF. Intra-lesional interleukin-2 for the treatment of in-transit melanoma. J Surg Oncol. 2011;104:711–7.
37. Weide B, Derhovanessian E, Pflugfelder A, et al. High response rate after intratumoral treatment with interleukin-2. Cancer. 2010;116:4139–46.
38. Temple-Oberle CF, Byers BA, Hurdle V, et al. Intra-lesional interleukin-2 therapy for in transit melanoma. J Surg Oncol. 2014;109:327–31.
39. Balch CM, Gershenwald JE, Soong SJ, et al. Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. J Clin Oncol. 2010;28:2452–9.
40. Wrightson WR, Wong SL, Edwards MJ, et al. Complications associated with sentinel lymph node biopsy for melanoma. Ann Surg Oncol. 2003;10:676–80.
41. Faries MB, Thompson JF, Cochran A, et al. The impact on morbidity and length of stay of early versus delayed complete lymphadenectomy in melanoma: results of the multicenter selective lymphadenectomy trial (MSLT-1). Ann Surg Oncol. 2010;17(2):3324–9.
42. Ollila D. Complete metastasectomy in patients with stage IV metastatic melanoma. Lancet Oncol. 2006;7:919–24.
43. Wright F, De Vito C, Langer B, Hunter, A and the Expert Panel on the Multidisciplinary Cancer Conference Standards. Multidisciplinary cancer conference standards: Available at http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=14320 .
44. Harpole Jr DH, Johnson CM, Wolfe WG, et al. Analysis of 945 cases of pulmonary metastatic melanoma. J Thorac Cardiovasc Surg. 1992;103:743–8.
45. Frenkel S, Nir I, Hendler K, et al. Long-term survival of uveal melanoma patients after surgery for liver metastases. Br J Ophthalmol. 2009;93:1042–6.
46. Sondak VK, Gibney GT. Indications and options for systemic therapy in melanoma. Surg Clin North Am. 2014;94:1049–58.
47. Sosman JA, Moon J, Tuthill RJ, et al. A phase-II trial of complete resection of stage IV melanoma: results of southwest oncology group (SWOG) clinical trial S9430. Cancer. 2011;117(20):4704–6.
48. Harrison Howard J, Thompson JF, Mozzillo N, et al. Metastasectomy for distant metastatic melanoma: analysis of data from the first multicenter selective lymphadenectomy trial (MSLT-I). Ann Surg Oncol. 2012;19(8):2547–55.
49. Khayat D, Rixe O, Martin G, et al. Surgical margins in cutaneous melanoma (2 cm versus 5 cm for lesions measuring less than 2.1-mmthick). Cancer. 2003;97:1941–6.
50. Cohn-Cedermark G, Rutqvist LE, Andersson R, et al. Long term results of a randomized study by the Swedish Melanoma Study Group on 2-cm versus 5-cm resection margins for patients with cutaneous melanoma with a tumour thickness of 0.8-2.0 mm. Cancer. 2000;89:1495–501.
51. Veronesi U, Cascinelli N. Narrow excision (1-cm margin): a safe procedure for thin cutaneous melanoma. Arch Surg. 1991;126:438–41.
52. Balch CM, Urist MM, Karakousis CP, et al. Efficacy of 2-cm surgical margins for intermediate-thickness melanomas (1 to 4 mm). Results of a multi-institutional randomized surgical trial. Ann Surg. 1993;218:262–7.
53. Balch CM, Soong SJ, Smith T, et al. (Investigators from the Intergroup Melanoma Surgical Trial). Long-term results of a prospective surgical trial comparing 2 cm vs. 4 cm excision margins for 740 patients with 1 - 4 mm melanomas. Ann Surg Oncol. 2001;8:101–8.
54. Thomas JM, Newton-Bishop J, A'Hern R, et al. (United Kingdom Melanoma Study Group, British Association of Plastic Surgeons, Scottish Cancer Therapy Network). Excision margins in high-risk malignant melanoma. N Engl J Med. 2004;350:757–66.
55. Chapman PB, Hauschild A, Robert C, BRIM-3 Study Group, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364:2507–16.
56. Hauschild A, Grob JJ, Demidov LV, et al. Dabrafenib in BRAF-mutated metastatic melanoma: a multicentre, open-label, phase 3 randomised controlled trial. Lancet. 2012;380(9839):358–65.

57. Flaherty KT, Robert C, Hersey P, et al. Improved survival with MEK inhibition in BRAF-mutated melanoma. N Engl J Med. 2012;367:107–14.
58. Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011;364:2517–26.
59. Kirkwood JM, Strawderman MH, Ernst-off MC, et al. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group trial EST 1684. J Clin Oncol. 1996;14:7–17.
60. Kirkwood JM, Ibrahim JG, Sondak VK, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol. 2000;18:2444–58.
61. Wheatley K, Ives N, Hancock B, et al. Does adjuvant interferon-alpha for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. Cancer Treat Rev. 2003;29(4):241–52.
62. Long GV, Stroyakovskiy D, Gogas H, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877–88.
63. Larkin J, Ascierto PA, Dreno B, et al. Combined vemurafenib and cobimetinib in BRAF-mutated melanoma. N Engl J Med. 2014;371(20):1867–76.
64. Wolchok JD, Kluger H, Callahan MK, et al. Nivolumab plus ipilimumab in advanced melanoma. N Engl J Med. 2013;369(2):122–33.
65. Topalian SL, Sznol M, McDermott DF, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. J Clin Oncol. 2014;32:1020–30.
66. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (Anti-PD-1) in melanoma. N Engl J Med. 2013;369(2):134–44.
67. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372:2521–32.
68. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373:23–34.
69. Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. N Engl J Med. 2015;372:320–30.
70. Pfeil AF, Leiter U, Buettner PG, et al. Melanoma of unknown primary is correctly classified by the AJCC melanoma classification from 2009. Melanoma Res. 2011;21(3):228–34.
71. Petrella T, Verna S, Spithoff K, et al. and the Melanoma Disease Site Group. Systemic adjuvant therapy for patients at high risk for recurrent melanoma: Updated guideline recommendations 2009. Available at https://www.cancercare.on.ca/toolbox/qualityguidelines/diseasesite/melanoma-ebs/
72. Eggermont AM, Spatz A, Robert C. Cutaneous melanoma. Lancet. 2014;383:816–27.
73. Eggermont AM, Suciu S, Testori A, et al. Ulceration and stage are predictive of interferon efficacy in melanoma: results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. Eur J Cancer. 2012;48:218–25.
74. Agrawal S, Kane 3rd JM, Guadagnolo GM, et al. The benefits of adjuvant radiation therapy after therapeutic lymphadenectomy for clinically advanced, high-risk, lymph node-metastatic melanoma. Cancer. 2009;115:5836–44.
75. Lee RJ, Gibbs JF, Proulx GM, et al. Nodal basin recurrence following lymph node dissection for melanoma: implications for adjuvant radiotherapy. Int J Radiat Oncol Biol Phys. 2000;46:467–74.
76. Burmeister BH, Henderson MA, Ainslie J, et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node filed relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. Lancet Oncol. 2012;13(6):589–97.
77. Guadagnolo BA, Prieto V, Weber R, et al. The role of adjuvant radiotherapy in the local management of desmoplastic melanoma. Cancer. 2014;120:1361–8.
78. Egger ME, Huber KM, Dunki-Jacobs EM, et al. Incidence of sentinel lymph node involvement in a modern, large series of desmoplastic melanoma. J Am Coll Surg. 2013;217:37–45.
79. Han D, Zager JS, Yu D, et al. Desmoplastic melanoma: is there a role for sentinel lymph node biopsy? Ann Surg Oncol. 2013;20:2345–51.

Chapter 14
Merkel Cell Carcinoma

Jennifer Racz, Anthony M. Joshua, Joan E. Lipa, Alexander Sun, and Frances C. Wright

Introduction

Merkel cell carcinomas (MCCs) are rare cutaneous neuroendocrine neoplasms that are clinically aggressive due to a relatively high local, regional, and distant metastatic recurrence potential [1]. These tumours behave in a more lethal fashion than melanoma and are associated with an overall 5-year survival rate between 30 and 64 % [2–5]. They are found most commonly in Caucasian (94 %), elderly patients, with the average age at presentation being 72 years [6–8]. The most common sites of involvement include the head and neck (46–48 %), followed by the extremities (35–38 %), and trunk (11–17 %) [6, 7]. Risk factors include extensive sun exposure, immunosuppression, and/or infection with the polyomavirus virus [7, 9–11].

J. Racz, M.D., M.B.A., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: jennifer.racz@gmail.com

A.M. Joshua, M.B.B.S., Ph.D., F.R.A.C.P.
Department of Medical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Anthony.joshua@uhn.ca

J.E. Lipa, M.D., M.Sc., F.R.C.S.C., F.A.C.S. • F.C. Wright, M.D., M.Ed., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: joan.lipa@sunnybrook.ca; frances.wright@sunnybrook.ca

A. Sun, M.D., F.R.C.P.C.
Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Alex.Sun@rmp.uhn.on.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_14

MCCs usually present as non-tender, rapidly growing, painless, red to violaceous intradermal papules or nodules that can reach considerable size. Given their relatively non-specific clinical presentation, diagnosis is often delayed leading to advanced disease at the time of diagnosis. The "AEIOU" acronym can be used to assist with diagnosis: A—asymptomatic, E—expanding, I—immunosuppressed, O—age >50 years, and U—ultraviolet-exposed fair skin [1]. Ultimately, diagnosis is established by excisional or punch biopsy demonstrating the characteristic small, round, blue cells with large prominent nuclei. Immunohistochemical analysis has been instrumental in identifying markers characteristic of MCC, facilitating its differentiation from other small round, blue cell tumours. Whereas cytokeratin-20 (CK-20) staining is positive in 89–100 % of MCCs, thyroid transcription factor-1 (TTF-1) is generally absent [1].

Presentation [5]	Prognosis [12] 5-Year overall survival (OS)
• Localized disease (66 %)	64 %
• Regional metastasis (27 %)	39 %
• Distant metastasis (7 %)	18 %

The American Joint Committee on Cancer AJCC 7th edition is the current recommended staging system for MCCs. Prognostically, patients who have pathologically proven node-negative disease have improved survival compared to those who are only evaluated clinically. As such, the current AJCC guidelines divide stages I and II into A and B substages based upon the method of nodal evaluation [12].

Management

Localized Merkel Cell Carcinoma [3, 13–15]

Work-up	Surgical excision (margins)	Lymph node assessment	Adjuvant therapy	Follow-up
• History and physical examination • Complete skin and lymph node examination • Biopsy (H + E, IHC) • No labs • Imaging studies at physician discretion	• Wide local excision (1–2 cm margins) to investing fascia • Mohs micrographic surgical excision with negative margins and then re-excision (0.5–1.0 cm margins)	• Discuss and offer SLNB	• Refer to radiation oncology for consideration of adjuvant RTX to the primary site • No role for systemic chemotherapy in the adjuvant or neoadjuvant setting	• History and physical exam every 3–6 months for 3 years and then every 6–12 months thereafter

H + E hematoxylin and eosin staining, *IHC* immunohistochemistry, *SLNB* sentinel lymph node biopsy, *RTX* radiation therapy

Regional Metastatic Merkel Cell Carcinoma [15–17]

Clinical scenario	Work-up[a]	Surgical approach
SLNB positive	• Imaging: – CT chest, abdomen, and pelvis – PET-CT – MRI[b]	• Completion lymphadenectomy (CLND) should be offered and discussed • Level I–III axillary lymph node dissection • Superficial and deep groin dissection • Observation (if patient refuses further surgery or not surgical candidate) • Refer to radiation oncology for treatment to primary site and nodal basin and medical oncology for assessment of adjuvant therapy/clinical trial; there may be a role for radiation to the nodal basin instead of CLND in some patients
Clinically positive lymph nodes	• FNA or core biopsy • Imaging: – CT chest, abdomen, and pelvis – PET-CT – MRI[b]	• Therapeutic lymphadenectomy should be offered and discussed • Refer to radiation and medical oncology for assessment of adjuvant therapy/clinical trial

SLNB sentinel lymph node biopsy, *FNA* fine-needle aspiration, *CLND* completion lymphadenectomy
[a]PET-CT is gaining importance and may be preferred in some instances
[b]MRI can be used if PET-CT is unavailable

Sentinel Lymph Node Biopsy

The single most important prognostic characteristic of clinically localized MCC is the presence or absence of occult nodal metastases [18, 19]. The incidence of sentinel node metastases in MCC ranges anywhere between 11 and 47 % and approximately 30 % of clinically node-negative patients will harbor micrometastatic disease [20–23]. Unfortunately, SLNB is associated with a high false-negative rate (~15 %) likely secondary to lymphatic dysfunction and/or the relatively high number of MCCs on the head and neck leading to multiplicity of nodes compared to other sites. Several factors have been associated with SLN positivity including (a) primary tumour size (25 % for tumours ≤2 cm vs. 45 % for tumours >2 cm), and (b) the presence of lymphovascular invasion (55 % for tumours with lymphovascular invasion vs. 4 % for tumours with no evidence of lymphovascular invasion) [24]. SLNB also has therapeutic implications as patients with a positive sentinel lymph node appear to be at significantly higher risk of distant metastasis and death from MCC and thus may benefit from additional treatment [3, 4, 20, 22, 25–31]. Although SLNB is associated with a significant improvement in MCC-specific survival when compared to wide-local excision alone, well-designed, prospective studies are required to clarify its role particularly given the availability of alternative treatment in the form of chemotherapy and/or radiation therapy [32].

Metastatic Merkel Cell Carcinoma

Distant Metastatic Merkel Cell Carcinoma [15]

Work-up	Surgical approach	Systemic therapy
• Imaging: – CT chest, abdomen, and pelvis – PET-CT – MRI • No specific labs	May be considered for patients with oligometastasis after multidisciplinary tumour board consultation [33] For palliation of symptoms such as bleeding, pain, intestinal obstruction, or perforation of intestinal metastases	• Refer to radiation and medical oncology for assessment of combination therapy ± clinical trial enrollment • Multi-agent chemotherapy: – Cyclophosphamide/doxorubicin/vincristine – Carboplatin/etoposide – Cisplatin/etoposide

Notes: Combining chemotherapy and radiation therapy may provide better palliation of advanced locoregional disease compared to chemotherapy alone

Adjuvant Therapy for Merkel Cell Carcinoma

Radiation Therapy for Merkel Cell Carcinoma

Study	Treatment	Conclusions	Comment
Mojica P et al. [34]	• Surgery ± adjuvant RTX to the primary site • *N* = 1187	• OS was significantly increased with adjuvant RTX vs. surgery alone	• SEER registry data; no information on RFS or DSS • RTX-treated patients significantly younger than surgery-alone patients
Clark et al. [35]	• Surgery + adjuvant RTX to the primary site and regional nodal basin vs. surgery alone or RTX alone • *N* = 110	• Combined therapy improved both local regional control and DFS but not DSS	• Retrospective review of head and neck cases only; a high percentage of cases with positive surgical margins (38 %) • No differentiation between surgical and RTX monotherapies
Lewis et al. [36]	• Surgery ± adjuvant RTX to the primary site and regional nodal basin • *N* = 1254	• Reduction in local and regional recurrence associated with combination therapy vs. surgery alone • Rates of distant metastasis and OS were not significantly different	• Meta-analysis • Rates of local (40 %) and nodal (56 %) recurrence in the surgery-alone cohort notably high, calling into question the relevance of the conclusions

(continued)

(continued)

Study	Treatment	Conclusions	Comment
Jouary T et al. [37]	• Surgery + RTX to the primary site and regional nodal basin vs. surgery + observation • *N* = 83	• Adjuvant RTX associated with improvement in regional recurrence compared to observation (10 % vs. 16.7 %); no improvement in OS	• RCT of patients with stage I disease • Prematurely closed due to a drop in recruitment with the advent of SLNB

RTX radiation therapy, *OS* overall survival, *DFS* disease-free survival, *DSS* disease-specific survival, *RFS* recurrence-free survival, *RCT* randomized controlled trial

Indications for Post-operative Radiation Therapy [15]

- Radiation to the Primary Site
  - Primary tumour >1 cm in diameter
  - Salvage operation for recurrent disease
  - Positive margins that cannot be surgically re-excised
- Radiation to the Nodal Basin
  - Absence of surgical assessment of lymph node basin
  - Positive sentinel node without completion of node dissection
  - Bulky nodal disease with multiple (4+ axillary and 10+ inguinal) lymph node metastases
  - Extracapsular spread

Systemic Chemotherapy for Merkel Cell Carcinoma

Although there is sparse literature on chemotherapeutic options for MCC, at most institutions chemotherapy is used with or without surgery and/or radiation for stage III (regional nodal disease) or stage IV (distant metastatic disease) [15, 38]. Available date from retrospective studies, however, does not suggest a prolonged survival benefit for adjuvant chemotherapy [39, 40]. Enrollment in clinical trials is encouraged whenever available and appropriate.

Referring to Medical Oncology

- All patients with histologically confirmed MCCs, other than those with localized disease, should be referred to medical oncology to (1) evaluate the risk of tumour recurrence; and (2) to establish the role of systemic chemotherapy. If any doubt exists regarding patient risk stratification, referral to medical oncology is warranted.

Referring to Radiation Oncology

- All patients with histologically confirmed MCCs should be referred to radiation oncology for consideration of adjuvant, neoadjuvant, or primary therapy.

Referring to Multidisciplinary Cancer Conference (MCC)

- All patients with a diagnosis of MCC should be discussed to confirm pathologic diagnosis, and evaluate the indications for adjuvant or therapy.

Toronto Pearls

- The multidisciplinary management of MCCs is the cornerstone of evidence-based treatment.

References

1. Senchenkov A, Moran SL. Merkel cell carcinoma: diagnosis, management, and outcomes. Plast Reconstr Surg. 2013;5:771e–8.
2. The Rockwell Merkel Cell Carcinoma Group. Merkel cell carcinoma: recent progress and current priorities on etiology, pathogenesis, and clinical management. J Clin Oncol. 2009;27:4021–6.
3. Allen PJ, Bowne WB, Jaques DP, et al. Merkel cell carcinoma: prognosis and treatment of patients from a single institution. J Clin Oncol. 2005;23:2300–9.
4. Bichakjian CK, Lowe L, Lao CD, et al. Merkel cell carcinoma: critical review with guidelines for multidisciplinary management. Cancer. 2007;110:1–12.
5. Lemos BD, Storer BE, Iyer JG, et al. Pathological nodal evaluation improves prognostic accuracy in Merkel cell carcinoma: analysis of 5823 cases as the basis of the first consensus staging system. J Am Acad Dermatol. 2010;63:751–61.
6. Albores-Saavedra J, Batich K, Chable-Montero F, Sagy N, Schwartz AM, Henson DE. Merkel cell carcinoma demographics, morphology, and survival based on 3870 cases: a population based study. J Cutan Pathol. 2010;37:20–7.
7. Agelli M, Clegg LX. Epidemiology of primary Merkel cell carcinoma in the United States. J Am Acad Dermatol. 2003;49:832–41.
8. Miller RW, Rabkin CS. Merkel cell carcinoma and melanoma: etiological similarities and differences. Cancer Epidemiol Biomarkers Prev. 1999;8:153–8.
9. Heath M, Jaimes N, Lemos B, et al. Clinical characteristics of Merkel cell carcinoma at diagnosis in 195 patients: the AEIOU features. J Am Acad Dermatol. 2008;58:375–81.
10. Engels EA, Frisch M, Goedert JJ, Biggar RJ, Miller RW. Merkel cell carcinoma and HIV infection. Lancet. 2002;359:497–8.
11. Penn I, First MR. Merkel's cell carcinoma in organ recipients: reports of 41 cases. Transplantation. 1999;68:1717–21.

12. Edge SB, Byrd DR, Darducci M, et al. Chap 30: Merkel cell carcinoma. In: Edge SB, Byrd DR, Darducci M, et al., editors. AJCC cancer staging manual. New York, NY: Springer; 2009.
13. Medina-Franco H, Urist MM, Fiveash J, et al. Multimodality treatment of Merkel cell carcinoma: case series and literature review of 1024 cases. Ann Surg Oncol. 2001;8:204–8.
14. Gillenwater AM, Hessel AC, Morrison WH, et al. Merkel cell carcinoma of the head and neck: effect of surgical excision and radiation on recurrence and survival. Arch Otolaryngol Head Neck Surg. 2001;127:149–54.
15. Merkel cell carcinoma. In: National Comprehensive Cancer Network, editors. NCCN Guidelines. Vol I. Fort Washington, PA: National Comprehensive Cancer Network; 2012.
16. Siva S, Byrne K, Seel M, et al. 18F-FDG PET provides high-impact and powerful prognostic stratification in the staging of Merkel cell carcinoma: a 15-year institutional experience. J Nucl Med. 2013;54(8):1223–9.
17. Hawryluk EG, O-Regan KN, Sheehy N, et al. Positron emission tomography/computed tomography imaging in Merkel cell carcinoma: a study of 270 scans in 97 patients at the Dana-Farber/Brigham and Women's Cancer Center. J Am Acad Dermatol. 2013;68:592–9.
18. Munoz IP, Pardo Masferrer J, Olivera Vegas J, Medina Montalvo MS, Jover Diaz R, Perez Casas AM. Merkel cell carcinoma from 2008 to 2012: reaching a new level of understanding. Cancer Treat Rev. 2013;39(5):421–9.
19. Tarantola TI, Vallow LA, Halyard MY, Weenig RH, Warschaw KE, Grotz TE, et al. Prognostic factors in Merkel cell carcinoma: analysis of 240 cases. J Am Acad Dermatol. 2013;68(3): 425–32.
20. McAfee WJ, Morris CG, Mendenhall CM, et al. Merkel cell carcinoma: treatment and outcomes. Cancer. 2005;104(8):1761–4.
21. Goessling W, McKee PH, Mayer RJ. Merkel cell carcinoma. J Clin Oncol. 2002;20(2): 588–98.
22. Hill AD, Brady MS, Coit DG. Intraoperative lymphatic mapping and sentinel lymph node biopsy for Merkel cell carcinoma. Br J Surg. 1999;86(4):518–21.
23. Morton DL, Thompson JF, Cochran AJ, et al. Sentinel-node biopsy or nodal observation in melanoma. N Engl J Med. 2006;355(13):1307–17.
24. Fields RC, Busam KJ, Chou JF, et al. Recurrence and survival in patients undergoing sentinel lymph node biopsy for Merkel cell carcinoma: analysis of 153 patients from a single institution. Ann Surg Oncol. 2001;18:2529–37.
25. Mehrany K, Otley CC, Weenig RH, et al. A meta-analysis of the prognostic significant of sentinel lymph node status in Merkel cell carcinoma. Dermatol Surg. 2002;28(2):113–7.
26. Lewis JM, Zager JS, Yu D, et al. Full-thickness grafts procured from skin overlying the sentinel lymph node basin: reconstruction of primary cutaneous malignancy excision defects. Ann Surg Oncol. 2008;15(6):1733–40.
27. Scoggins CR, Martin RC, Ross MI, et al. Factors associated with false-negative sentinel lymph node biopsy in melanoma patients: results from a prospective randomized trial. Ann Surg Oncol. 2009;16 Suppl 1:3.
28. Gupta SG, Wang LC, Penas PF, et al. Sentinel lymph node biopsy for evaluation and treatment of patients with Merkel cell carcinoma: the Dana-Farber experience and meta-analysis of the literature. Arch Dermatol. 2006;142(6):685–90.
29. Pectasides D, Pectasides M, Economopoulos T. Merkel cell cancer of the skin. Ann Oncol. 2006;17(10):1489–95.
30. Sandel HD, Day T, Ricahrdson MS, et al. Merkel cell carcinoma: does tumour size or depth of invasion correlate with recurrence, metastasis, or patient survival? Laryngoscope. 2006;116(5):791–5.
31. Wagner JD, Evdokimow DZ, Weisberger E, et al. Sentinel node biopsy for high-risk nonmelanoma cutaneous malignancy. Arch Dermatol. 2004;140(1):75–9.
32. Kachare SD, Wong JH, Vohra NA, Zervos EE, Fitzgerald TL. Sentinel lymph node biopsy is associated with improved survival in Merkel cell carcinoma. Ann Surg Oncol. 2014;21:1624–30.
33. Gonzalez RJ, Padhya TA, Cherpelis BS, et al. The surgical management of primary and metastatic Merkel cell carcinoma. Curr Probl Cancer. 2010;34(1):77–96.

34. Mojica P, Smith D, Ellenhorn JD. Adjuvant radiation therapy is associated with improved survival in Merkel cell carcinoma of the skin. J Clin Oncol. 2007;25:1043–7.
35. Clark JR, Veness MJ, Gilbert R, et al. Merkel cell carcinoma of the head and neck: is adjuvant radiotherapy necessary? Head Neck. 2007;29(3):249–57.
36. Lewis KG, Weinstock MA, Weaver AL, Otley CC. Adjuvant local irradiation for Merkel cell carcinoma. Arch Dermatol. 2006;142:693–700.
37. Jouary T, Leyral C, Dreno B, et al. Adjuvant prophylactic regional radiotherapy versus observation in stage I Merkel cell carcinoma: a multicentric prospective randomized study. Ann Oncol. 2012;23:1074–80.
38. Desch L, Kunstfeld R. Merkel cell carcinoma: chemotherapy and emerging new therapeutic options. J Skin Cancer. 2013;2013:327150.
39. Gameski KM, Nghiem P. Merkel cell carcinoma adjuvant therapy: current data support radiation but not chemotherapy. J Am Acad Dermatol. 2007;57:166–9.
40. Tai P. Merkel cell cancer: update on biology and treatment. Curr Opin Oncol. 2008;20:196–200.

Chapter 15
Multidisciplinary Cancer Conferences

Trevor D. Hamilton, Savtaj S. Brar, Nicole J. Look Hong, Robin McLeod, and Frances C. Wright

Introduction

Collaborative multidisciplinary care can take several formats depending on the practice environment and resources of an institution. The most common reported examples of integrated multidisciplinary care are multidisciplinary cancer conferences (MCCs) and multidisciplinary clinics (MDCs).

MCCs are regularly scheduled meetings where health care providers assemble to collaboratively discuss the management of individual cancer patients. The primary purpose of MCCs is to ensure that all appropriate diagnosis and treatment options are prospectively considered for each patient discussed. MCCs have been widely used in the USA, Australia, Europe, Canada, and the UK [1–5]. MDCs promote inter-specialty communication, by allowing a patient to consult with several health care providers in a single visit. The goal of both MCCs and MDCs is to facilitate prompt and comprehensive patient management and to provide a convenient, supportive, and educational environment for all involved [6].

T.D. Hamilton, M.D., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: trevordhamilton@gmail.com

S.S. Brar, M.D., M.Sc., F.R.C.S.C. • N.J. Look Hong, M.D., M.Sc., F.R.C.S.C.
R. McLeod, M.D., F.R.C.S.C., F.A.C.S. • F.C. Wright, M.D., M.Ed., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: sbrar@mtsinai.on.ca; Nicole.LookHong@sunnybrook.ca;
robin.mcleod@cancercare.on.ca; frances.wright@sunnybrook.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_15

MCC Structure

The available evidence is unable to provide quality indicators to determine the success or failure of an MCC. However, the following structural and functional elements, or their equivalents, are common to several described international MCCs.

Role	Responsibilities
Participants	• Present patient cases and actively provide expert opinion in patient diagnosis and management • Feedback to patients the results of MCC discussion and carry out discussed plan • Recording of MCC discussion in medical record
MCC Coordinator	• Establish the MCC participants, location, patients to be discussed at each meeting • Communicate with MCC participants to ensure ongoing attendance and participation • Organize attendance of key personnel and resources (e.g., videoconferencing) for each patient case • Lead the collection and recording of ***conference-specific*** and ***case-specific*** data[a]
MCC Chair	• Facilitate the MCC meeting to ensure efficient use of time and resources • Allocate appropriate time to discuss each patient • Maintain patient confidentiality

[a]MCCs and their patient discussions should be meticulously documented to ensure consistent patient care and to facilitate ongoing audit

Quality indicators to ensure well-structured MCC

- Conference-specific indicators:
  - Date and time of MCC
  - Attendees
  - Patients discussed
- Case-specific indicators:
  - Patient name, medical record number, and presenting physician
  - Diagnosis and clinical question(s)
  - Clinical data presented
  - Recommendations made by MCC participants

The ***frequency*** of MCCs may vary from **weekly** to **biweekly**, depending on the institutional volume of cancer patients and need for consultative services at an institution [1].

Additional research is being conducted to improve the organization and facilitation of MCCs. Some evidence suggests that developing MCC checklists that help prepare cases, guide discussions, and document recommendations improves the quality of decision-making [7]. As well, the importance of organizing support, recording of disagreements, and the use of nurse specialists as patient advocates may help to ensure high-quality patient care in MCCs [8].

Landmark Publications

Multidisciplinary care, including MDCs and MCCs, has been suggested to have many benefits, as shown below in selected references. Strategies for improving access to MCCs and evidence for the utility and feasibility of videoconferencing are included, as this is a medium used to link smaller, less-equipped hospitals with appropriate clinical expertise and resources. There are no randomized controlled trials definitively linking multidisciplinary forums with changes in outcomes.

Benefits of Multidisciplinary Clinics (MDCs)

Study	Methods	Results
Gabel et al. [6]	• Retrospective before–after series of **breast cancer** patients in the USA • N1 = 162 patients before MDC • N2 = 177 patients after MDC • Measured outcomes: – Timeliness of treatment before and after institution of a breast MDC – Patient satisfaction	• With MDC: – Increased patient satisfaction ($p < 0.001$) – Decreased time between initial diagnosis and treatment initiation ($p < 0.0008$)
Conron et al. [9]	• Retrospective case series of **lung cancer** patients in Australia • N = 431 patients • Adherence to best guidelines after establishment of MDC • Measured outcomes: • Timeliness of care	• 84–100 % compliance to current international guidelines, dependent on stage and histologic subtype • Facilitated diagnosis and access to care with MDC
Pawlik et al. [10]	• Prospective cohort study of **pancreatic cancer** patients at a single institution in the USA • N = 203 patients • Institution of single-day MDC • Measured outcomes: – Recommended management – Clinical stage	• 23.6 % change in recommended management • 18.7 % change in clinical stage
Yopp et al. [11]	• Retrospective before–after series of **HCC** patients at a single institution in the USA • N = 355 patients • Implementation of MDC • Measured outcomes: – Overall Survival – Timeliness of care – Symptoms	• Shorter time from diagnosis to treatment ($p = 0.002$) • Fewer symptoms at presentation ($p = 0.01$) • Earlier stage at tumor presentation ($p = 0.0003$) • Median survival more than doubled ($p = 0.005$)

MDC multidisciplinary clinic, *HCC* hepatocellular carcinoma

Changes in Patient Management (MCCs)

Study	Methods	Results
Chang et al. [12]	• Retrospective case series of **breast cancer** patients in the USA • N = 77 breast lesions • Measured outcomes: – Concordance of treatment recommendations before and after presentation at MCC	• 55 % concordance in treatment plan before and after MCC presentation
Abraham et al. [13]	• Cross-sectional study of **stage II/III colorectal cancer** patients in the USA • N = 197 patients • Measured outcomes: – Adherence to national treatment guidelines	• Presentation at MCC predicted receipt of recommended treatment (OR 3.6)
Newman et al. [14]	• Retrospective case series of **breast cancer** patients in the USA • N = 149 patients • Measured outcomes: – Changes in medical and surgical management after presentation at MCC	• Overall 52 % of patients had a change in surgical management
Santillan et al. [15]	• Retrospective case series of **thin melanoma and melanoma in situ** patients in the USA • N = 420 patients • Measured outcomes: – Changes in diagnosis and staging from referring pathologic diagnosis before and after presentation to an MCC	• 4 % Pathologic discordance • 24 % Change in tumor staging • 12 % Change in excision margins • 16 % Change in sentinel lymph node management
Boxer et al. [16]	• Retrospective case series of **lung cancer** patients in Australia • N = 988 patients • Measured outcomes: – Treatment differences in patients discussed at MCCs or not	• No difference in surgical treatment • More patients received RT (66 % vs. 33 %), chemo (46 % vs. 29 %), palliative care (66 % vs. 53 %) if discussed at MCCs ($p \leq 0.001$)

MCC multidisciplinary cancer conference, *RT* radiation therapy

Improved Outcomes: Local Control or Survival (MDC, MCC)

Study	Methods	Results
Birchall et al. [17]	• Retrospective before–after series of 2 cohorts of head and neck cancer patients in England • N1 = 566 patients (1997) • N2 = 727 patients (2000) • Measured outcomes: – 2 year survival before and after institution of multidisciplinary clinic	• Correlation between improved survival and assessment at multidisciplinary clinic (HR 0.7, $p = 0.02$) • Overall no change in 2 year survival
Forrest et al. [18]	• Retrospective before–after series of 2 cohorts of stage IIIb lung cancer patients in Scotland • N1 = 117 patients • N2 = 126 patients • Measured outcomes: – Median survival before and after institution of multidisciplinary team	• Increased median survival before (3.2 months) and after (6.6 months) institution of multidisciplinary team ($p < 0.0001$)
Burton et al. [19]	• Retrospective before–after series of rectal cancer patients in the UK • N1 = 298 patients • N2 = 98 patients • Measured outcomes: – Rate of positive CRM before and after mandatory MRI-based MCC discussion	• Reduced + CRM after mandatory MRI-based MCC (12.5 % vs. 7 %)
Lordan et al. [20]	• Prospective cohort study of patients with hepatic metastases from colorectal cancer in the UK • N = 331 patients • Measured outcomes: – 1, 3, and 5 year overall survival and DFS for patients referred by a multidisciplinary team with and without a liver surgeon	• No difference in DFS • Increased overall survival in patients referred by a multidisciplinary team including a liver surgeon ($p = 0.0001$)

MCC multidisciplinary cancer conference, *CRM* circumferential resection margin, *DFS* disease free survival

Improving Access to MCCs

Study	Methods	Results
Brar et al. [21]	• Prospective analysis of MCCs in Ontario over 3 year period • N1 = 4695 patients (2009) • N2 = 4991 patients (2010) • N3 = 5702 patients (2011) • Measured outcomes: – Criteria satisfaction score – MCC frequency – Number of patients discussed	• Trend towards increased number of MCCs and patients discussed • Improved criteria satisfaction score over time ($p \leq 0.001$)

Videoconferencing MCCs

Study	Methods	Results
Stalfors et al. [22]	• Head and neck cancer patients in Sweden • N = 80 patients • Measured outcomes: – Concordance before and after presentation with: TNM classification Treatment plan	• 91 % Concordance of classification and treatment plan using telemedicine and face to face meeting
Gagliardi et al. [23]	• General surgery cancer patients in Canada • N = 6 observed videoconferenced MCCs • 11 interviews • Measured outcomes: – Thematic analysis of observation and interview transcripts	• Facilitated collective decision making • Improved awareness of evidence, appropriate care delivery, and continuity of care

Referring to Multidisciplinary Cancer Conference (MCC)

The literature does not provide evidence to guide who should attend a MCC or which patients should or should not be presented. Referral of patients and the attendance of key participants vary by the anatomic site/tumor subtype under discussion, and by the available expertise at each institution. The following guidelines have been proposed by Cancer Care Ontario (CCO) [24]:

MCC attendees	Suggested cases
• Medical/Radiation/Surgical Oncologist • Pathologist • Radiologist • Orthopedic Surgeon (sarcoma) • Gastroenterologist/Endoscopist (gastrointestinal) • Otolaryngologist (head and neck) • Dermatologist (melanoma) • Interventional Gastroenterologist (hepatobiliary) • Interventional Radiologist (hepatobiliary) • Endocrinologist (neuroendocrine) • Nuclear Medicine (neuroendocrine) • +/– nursing, genetics, social work, palliative care, plastic/reconstructive surgeon • +/– clinical trials representative	• Locally advanced tumors (e.g., satellite or in-transit melanoma, stage III breast cancer) • Newly diagnosed, rare case presentations (e.g., inflammatory breast cancer, atypical nevi, unknown primary) • Genetic syndromes • Potential combined modality management requiring treatment sequencing (e.g., gastric, esophageal, rectal, extremity/retroperitoneal sarcoma) • Metastatic, synchronous, progressive, recurrent or treatment-refractory cases • Uncertainty in endoscopic, pathologic or radiologic identification or staging • Controversial or new evidence for diagnosis or treatment • Any patient being considered for transplantation • Any patient being considered for clinical trials

Toronto Pearls

Starting an MCC:

- Encourage **early** involvement of regional and institutional administrators to promote funding and access to needed resources (e.g., videoconferencing equipment, technical support, MCC coordinator).
- Engage involved health care providers (medical/radiation oncologist, pathologists, radiologists) to establish an institutional and/or disease-specific **champion**, who may be willing to be MCC chair.
- Establish and publicize institutional **terms of reference** to guide frequency, attendance requirements, and expectations for the MCC coordinator, chair, and participants.

Maintaining Productive MCCs:

- Ensure a defined clinical question to guide radiology and pathology input and to direct the MCC discussion.
- Choose an engaged and dynamic chair to efficiently guide patient discussions.
- Confer with regional medical and radiation oncologists (if not available at an institution) to ensure comprehensive evidence-based care.
- Ensure comprehensive documentation of patient discussions and MCC attendants to maintain provincial/national standards of cancer care and enable attainment of financial remuneration, if available.

References

1. American College of Surgeons, Commission on Cancer. Cancer program standards. Chicago, IL: American College of Surgeons; 2012, released 2014. Available at https://www.facs.org/quality-programs/cancer/coc/standards.
2. Australia C. Multidisciplinary meetings for cancer care: a guide for health service providers. Camperdown, NSW: National Breast and Ovarian Cancer Centre; 2005. Available at http://canceraustralia.gov.au.
3. Balmey R, Cataliotti L. European society of mastology (EUSOMA). The requirements of a specialist breast unit. Eur J Cancer. 2000;36:2288–93.
4. Wright FC, DeVito C, Langer B, et al. Multidisciplinary cancer conferences: a systematic review and development of practice standards. Eur J Cancer. 2007;43:1002–10.
5. Department of Health. National Health Service: Manual for cancer services 2004. Topic 2A: The generic multidisciplinary team (MDT). London, UK: DH Publications; 2004. Available at: http://www.dh.gov.uk/publications.
6. Gabel M, Hilton NE, Nathanson SD. Multidisciplinary breast cancer clinics. Do they work? Cancer. 1997;79(12):2380–4.
7. Lamb BW, Sevadalis N, Vincent C, et al. Development and evaluation of a checklist to support decision making in cancer multidisciplinary team meetings: MDR-QuIC. Ann Surg Oncol. 2012;19:1759–65.
8. Lamb BW, Taylor C, Lamb JN, et al. Facilitators and barriers to teamworking and patient centeredness in multidisciplinary cancer teams: findings of a national study. Ann Surg Oncol. 2013;20:1408–16.
9. Conron M, Phuah S, Steinfort D, et al. Analysis of a multidisciplinary lung cancer practice. Int Med J. 2007;37:18–25.
10. Pawlik TM, Laheru D, Hruban RH, et al. Evaluating the impact of a single-day multidisciplinary clinic on the management of pancreatic cancer. Ann Surg Oncol. 2008;15(8):2081–8.
11. Yopp AC, Mansour JC, Beg MS, et al. Establishment of a multidisciplinary hepatocellular carcinoma clinic is associated with improved clinical outcome. Ann Surg Oncol. 2014;21(4):1287–95.
12. Chang JH, Vines E, Bertsch H, et al. The impact of a multidisciplinary breast cancer center on recommendations for patient management: the University of Pennsylvania experience. Cancer. 2001;91(7):1231–7.
13. Abraham NS, Gossey JT, Davila JA, et al. Receipt of recommended therapy by patients with advanced colorectal cancer. Am J Gastroenterol. 2006;101:1320–8.
14. Newman EA, Guest AS, Helvie MA, et al. Changes in surgical management resulting from case review at breast cancer multidisciplinary tumour board. Cancer. 2006;107(10):2346–51.
15. Santillan AA, Marzban SS, Crespo G, et al. Pathology review of thin melanoma and melanoma in situ in a multidisciplinary melanoma clinic: impact on treatment decisions. J Clin Oncol. 2010;28(3):481–6.
16. Boxer MM, Vinod SK, Shafiq J, et al. Do multidisciplinary team meetings make a difference in the management of lung cancer? Cancer. 2011;117:5112–20.
17. Birchall M, Bailey D, King P. South West Cancer Intelligence Service Head and Neck Tumour Panel. Effect of process standards on survival of patients with head and neck cancer in the south and west of England. Br J Cancer. 2004;91(8):1477–81.
18. Forrest LM, McMillan DC, McArdle CS, et al. An evaluation of the impact of a multidisciplinary team, in a single centre, on treatment and survival in patients with inoperable non-small-cell lung cancer. Br J Cancer. 2005;93(9):977–8.
19. Burton S, Brown G, Daniels IR, et al. MRI directed multidisciplinary team preoperative treatment strategy: the way to eliminate positive circumferential margins? Br J Cancer. 2006;94:351–7.

20. Lordan JT, Karanjia ND, Quiney N, Fawcett WJ, Worthington TR. A 10 year study of outcome following hepatic resection for colorectal liver metastases: the effect of evaluation in a multidisciplinary team setting. Eur J Surg Oncol. 2009;35(3):302–6.
21. Brar SS, Provvidenza C, Hunter A, et al. Improving multidisciplinary cancer conferences: a population-based intervention. Ann Surg Oncol. 2014;21:16–21.
22. Stalfors J, Edstrom S, Bjork-Eriksson T, et al. Accuracy of tele-oncology compared with face-to-face consultation in head and neck cancer case conferences. J Telemed Telecare. 2001;7:338–43.
23. Gagliardi AR, Wright FC, Anderson MA, Davis D. The role of collegial interaction in continuing professional development. J Contin Educ Health Prof. 2007;27(4):214–9.
24. Cancer Care Ontario. Multidisciplinary Cancer Conferences (MCCs): Disease site attendance criteria and patient discussion guidance. March 2010. Updated January 2014. Available at: http://cancercare.on.ca/common/pages/UserFile.aspx?fileId=63113.

Chapter 16
Neuroendocrine Tumors (GastroEnteroPancreatic)

Usmaan Hameed, Moises Cukier, Julie Hallet, Calvin H.L. Law, Corwyn Rowsell, and Simron Singh

Introduction

In the USA, the prevalence of neuroendocrine tumors (NETs) is 35 per 100,000 [1]. An increasing incidence (per 100,000 population per year) has been reported in multiple recent population-based studies throughout the world. In Ontario, Canada, the incidence of NETs went from 2.48 (1994) to 5.86 (2009) [2]. This increase is likely explained by better detection, diagnosis, and classification.

U. Hameed, M.D., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Usmaan.Hameed@nygh.on.ca

M. Cukier, M.D.
Department of Surgical Oncology, National Cancer Institute, Panama City, Panama
e-mail: moisescukier@gmail.com

J. Hallet, M.D., M.Sc., F.R.C.S.C. • C.H.L. Law, M.D., M.P.H., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: julie.hallet@sunnybrook.ca; Calvin.Law@sunnybrook.ca

C. Rowsell, M.D., F.R.C.P.C., F.C.A.P.
Department of Laboratory, Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
e-mail: Corwyn.Rowsell@sunnybrook.ca

S. Singh, M.D., M.P.H., F.R.C.P.C.
Department of Medicine, University of Toronto, Toronto, ON, Canada
e-mail: Simron.Singh@sunnybrook.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_16

Distribution and survival of gastroenteropancreatic NET [5]

Site	Frequency	Overall survival (5 year OS)
Jejunum/Ileum	31 %	73 %
Rectum	21 %	87 %
Colon[a]	22 %	64 %
Pancreas	16 %	48 %
Gastric	9 %	67 %

[a]This group includes appendiceal NET

For the purpose of this chapter, we focus on well-differentiated gastroenteropancreatic (GEP) NETs. Primary pulmonary, thyroid, or thymic NETs, gynecological and poorly differentiated NETs are beyond the scope of this chapter.

Pathological Classification, Grading, and Staging

Classification systems have been) evolving in NET as knowledge about their biologic behavior has increased. Traditional classifications based solely on site (foregut, midgut, hindgut), biochemical properties, or granule staining techniques have been rendered obsolete. The World Health Organization (WHO) proposed a prognosis-oriented classification system based on both staging and grading information (revised in 2010), with a stage-independent system based solely on proliferation [3, 4]. The 2010 WHO classification was based on the European Neuroendocrine Tumor Society (ENETS) grading system (G1, G2, G3) [5], which is also supported by the North American Neuroendocrine Tumor Society (NANETS) [6].

Two staging systems are currently available. The ENETS recently suggested a tumor-node-metastasis (TNM) staging system, which has been widely adopted in Europe [5]. The 7th edition of the American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) classification includes, for the first time, their TNM staging classification for GEP-NETs [7], which differs from the one proposed by ENETS (specifically in pancreatic and appendiceal NETs), and only applies to well-differentiated NETS. The College of American Pathologists (CAP) has based their protocol on the AJCC classification.

- Given the changes in classification and the presence of competing TNM staging systems, it is essential that pathology reports clearly identify the system that was used to classify, grade, and stage the tumor.
- Survival for GEP-NETs is dictated by (1) grade and (2) primary tumor localization, and (3) metastases [1, 2].
- Minimal dataset for pathology reporting of NET include: anatomic site of primary tumor, presence of multicentric disease, IHC for chromogranin and synaptophysin, grade (proliferation rate assessed by Ki-67 and mitotic rate), presence of other non-neuroendocrine components, lymph node metastases [8].

Classification and grading systems for NETs

Classification system		General criteria	Comments
WHO 2010	NET G1	• ≤ 2 % Ki-67 index • < 2 mitoses/10 hpf	• Stage and site independent • Based on ENETs grading system • If Ki-67 index and MR are discordant, classify according to the higher of the two parameters • NEC may be further classified morphologically as small or large cell type
	NET G2	• 3–20 % Ki-67 index • 2–20 mitoses/10 hpf	
	NEC	• > 20 % Ki-67 index • > 20 mitoses/10 hpf	

WHO World Health Organization classification, *WD* well-differentiated, *PD* poorly differentiated, *NET* Neuroendocrine tumor, *NEC* Neuroendocrine carcinoma, *G1* Grade 1, *G2* Grade 2

Characteristics of GEP NETs

Site	Synchronous malignancies	Risk of lymph node metastases	Risk of distant metastases		Genetic cancer syndrome associated
			Liver	Other	
Duodenal	–	–	Rare	–	MEN-1/ZES (40 %), NF-1
Ileum/jejunum	18 %	70 %	50–70 %	–	–
Rectum	25 %			Bone	–
• < 1 cm		2 %	< 1 %		
• 1–2 cm		10–15 %	5 %		
• > 2 cm		60–80 %	10 %		
Colon	20 %	–	–	Bone	–
Pancreas	9 %	–		–	
• Nonfunctional			60 %		MEN-1 (25 %)
• Insulinoma			10 %		MEN-1 (5 %)
• Gastrinoma			60 %		MEN-1 (25 %)
• Glucagonoma			80 %		MEN-1 (15 %)
• VIPoma			80 %		MEN-1 (10 %)
Gastric	20 %			Bone	MEN-1 (10 %)
• Type 1		2.5 %	2.5 %		MEN-1/ZES (100 %)
• Type 2		30 %	10 %		
• Type 3		70 %	70 %		
• Type 4					
Appendix	18 %	–	–	–	–

MEN-1 multiple endocrine neoplasia syndrome type 1, *ZES* Zollinger–Ellison syndrome, NF-1 neurofibromatosis type 1

Special Notes

- Small bowel NETs are multiple in up to 30 % of cases.
- The risk of synchronous or metachronous neoplasia in patients with GEP-NETs is approximately 40 %, with half of those synchronous neoplasia being an adenocarcinoma in the colon, rectum, or stomach [9, 10]. It has recently been suggested that this association could be related to higher detection rate of NET in patients with other cancers as a result of surveillance strategies.

Classification and Management of Gastroenteropancreatic NETs

Gastric NETs

Type	%	Notes	Association	5Y-OS (%)
I	75	Small, superficial, often multiple	Chronic Atrophic Gastritis, hypergastrinemia	95
II	4	Small, superficial, almost always multiple	MEN-I associated ZES, hypergastrinemia	70–90
III	20	Aggressive	Sporadic, normal gastrin levels	<35
IV	1	Aggressive, Poorly Differentiated	Poorly differentiated, neuroendocrine cells within tumor, indistinguishable from adenocarcinoma	< 25

ZES Zollinger–Ellison syndrome, *5Y-OS* 5-year overall survival

Workup	Surgical treatment	Perioperative management	Follow-up
• Labs: – Serum CgA – 24 h urine 5-HIAA – Fasting serum gastrin[a] • Imaging: – CT C/A/P – EUS if considering endoscopic resection	• Type 1 or 2, < 2 cm: – Endoscopic resection (if feasible and no extension into muscularis propria on EUS) • Type 2: – May require more aggressive gastric resection, resection of gastrinoma	• Preoperative: – If carcinoid syndrome or elevated 5-HIAA: – Octreotide 200 to 600 μg sc in divided doses 3–5 days pre-op – Intraoperative octreotide drip	• < 1 year (3–6 months): – CgA – 5-HIAA, if initially elevated – CT C/A/P or MRI – If results are abnormal, octreotide scan or MIBG – OGD if total gastrectomy not performed
	• Type III, IV, ≥ 2 cm, recurrent or ≥ 6 polyps: – Gastrectomy (partial or total) and lymphadenectomy	• Adjuvant treatment: – Ki-67 > 20 %: Cisplatin and Etoposide – Octreotide—if progression or elevated 5-HIAA	• > 1 year (6–12 months) – CgA – 5-HIAA[a] – CT A/P or MRI – Gastroscopy

CgA Chromogranin A, *5-HIAA* 5-Hydroxyindoleacetic Acid, *MIBG* Iodine-131-meta-iodobenzylguanidine, *C/A/P* chest, abdomen, and pelvis

[a]Proton pump inhibitors should be stopped at least 7 days prior to gastrin level measurement

Duodenal NETs

<table>
<tr><th>Workup</th><th>Surgical treatment</th><th>Perioperative management</th><th>Follow-up</th></tr>
<tr><td rowspan="2">• Labs:
– Serum CgA
– 24 h urine 5-HIAA
• Imaging:
– CT scan C/A/P
– EUS if considering endoscopic resection</td><td>• Can consider endoscopic resection if:
• < 2 cm
• Confined to mucosa or submucosa on EUS
• No lymphadenopathy on imaging</td><td rowspan="2">• Insufficient data to recommend adjuvant therapy in completely resected locoregional disease
• Octreotide LAR: if progression or elevated 5-HIAA
• Octreotide short-acting: can be added to LAR for symptom control in refractory cases</td><td>• < 1 year
– CgA 3–6 months
– 5-HIAA 3–6 months[a]
– CT C/A/P 6–12 months
– If results are abnormal, octreotide scan or MIBG</td></tr>
<tr><td>• Segmental resection
• Avoid aggressive resection with pancreaticoduodenectomy if possible</td><td>• > 1 year (6–12 months):
– Serum CgA
– 5-HIAA levels[a]
– CT scan A/P</td></tr>
</table>

CgA Chromogranin A, *5-HIAA* 5-Hydroxyindoleacetic Acid, *MIBG* Iodine-131-meta-iodobenzylguanidine, *C/A/P* chest, abdomen, and pelvis
[a]If functional or 5-HIAA elevated at diagnosis

Special Notes

- Although liver metastases are rare in duodenal NETs, lymphadenectomy is advised if imaging suggests lymph node involvement
- 60 % 5 year overall survival
- 5 Types of duodenal NETs are described:
  - Sporadic or occurring in the setting of MEN-1/ZES (most common)
  - Somatostatinomas occurring near ampulla, associated with NF-1
  - Gangliocytic paraganglioma
  - Nonfunctional NET containing serotonin, gastrin, or calcitonin positive cells
  - Neuroendocrine carcinoma

Ileal/Jejunal NETs

Workup	Surgical treatment	Perioperative management	Follow-up
• **Labs**: – Serum CgA – 24 h urine 5-HIAA • **Imaging**: – CT C/A/P	• Segmental resection with lymphadenectomy • General recommendations: – Inspect and palpate the entire small bowel looking for additional tumors – If found incidentally, resect the primary including lymphadenectomy, even if clearly metastatic (survival benefit) [11]. – Consider cholecystectomy at the time of surgery (potential for long-term use of somatostatin analogs and possible embolization for liver metastases)	• Insufficient data to recommend adjuvant therapy in completely resected locoregional disease • Octreotide LAR: if progression or elevated 5-HIAA • Octreotide short-acting: can be added to LAR for symptom control in refractory cases.	• < 1 year – CgA (3–6 months) – 5-HIAA (3–6 months) – CT C/A/P (3–12 months) – If results are abnormal, octreotide scan or MIBG scintiscan • > 1 year (every 6–12 months): – Serum CgA – 5-HIAA levels, for all – CT scan A/P

CgA Chromogranin A, *5-HIAA* 5-Hydroxyindoleacetic Acid, *MIBG* Iodine-131-meta-iodobenzylguanidine, *C/A/P* chest/abdomen/pelvis

Colonic NETs

Workup	Surgical treatment	Perioperative management	Follow-up
• Labs: – Serum CgA – 24 h urine 5-HIAA (rarely positive) • Imaging: – CT C/A/P • Colonoscopy	• Endoscopic resection + tattooing if: – < 2 cm – Limited to mucosa/submucosa – Technically feasible	• Insufficient data to recommend adjuvant therapy in completely resected locoregional disease • Octreotide LAR: if progression or elevated 5-HIAA • Octreotide short-acting: can be added to LAR for symptom control in refractory cases	• < 2 cm resected with negative margins: no follow-up required • < 1 year (every 3–6 months): – CgA – 5-HIAA, if initially elevated – CT C/A/P +/- MRI – If results are abnormal, octreotide scan or MIBG
	• Colectomy (total or partial): – Same oncological principles as applied to colonic adenocarcinoma		• > 1 year (every 6–12 months) – CgA – 5-HIAA[a] – CT A/P or MRI

CgA Chromogranin A, *MIBG* Iodine-131-meta-iodobenzylguanidine, *5-HIAA* 5-Hydroxyindoleacetic Acid, *C/A/P* chest/abdomen/pelvis

[a] If functional or 5-HIAA elevated at diagnosis

Appendiceal NETs

Workup	Surgical treatment	Perioperative management	Follow-up (F/U)
• Labs: – Serum CgA – 24 h urine 5-HIAA • Imaging: – CT C/A/P • Colonoscopy	• Appendectomy only if all of the following: • ≤1 cm • Tip/body of appendix • Margins negative • No LVI or invasion into mesoappendix • Ki-67 < 2 %	• Insufficient data to recommend adjuvant therapy in completely resected locoregional disease • Octreotide LAR: if progression or elevated 5-HIAA • Octreotide short-acting: can be added to LAR for symptom control in refractory cases.	• Well-differentiated NET G1 and appendectomy alone: – No need for F/U • < 1 year (every 3–6 months) – CgA – 5-HIAA, for all – CT scan – If results are abnormal, octreotide scan or MIBG
	• Right Hemicolectomy + lymphadenectomy (any of the following): • ≥2 cm • Base of the appendix with positive margin • LVI or invasion into mesoappendix • Ki-67 index > 5 % • Mixed histology		• > 1 year (every 6–12 months): – CgA – 5-HIAA[a] – CT A/P or MRI

CgA Chromogranin A, *MIBG* Iodine-131-meta-iodobenzylguanidine, *5-HIAA* 5-Hydroxy-indoleacetic Acid, *C/A/P*: chest/abdomen/pelvis
[a] If functional or 5-HIAA elevated at diagnosis

Rectal NETs

Workup	Surgical treatment	Perioperative management	Follow-up
• Labs: – Serum CgA • Imaging – CT C/A/P – EUS and/or pelvic MRI • Colonoscopy • Preoperative: – Carcinoid syndrome is uncommon – Hormonal production for rectal is rare, most commonly histamine.	• Transanal Excision if: – < 2 cm in size – Distal/mid rectum – No lymph node involvement	• Octreotide LAR: – If progression or elevated 5-HIAA	• < 1 year (every 3–6 months) – CgA – CT C/A/P – If results are abnormal, octreotide scan or MIBG – Colonoscopy as per colorectal cancer recommendations
	• Total mesorectal excision (similar oncological principles applied to rectal adeno-carcinomas)		• > 1 year (every 6–12 months): – Serum CgA – CT scan A/P – Colonoscopy as per colorectal cancer recommendations

CgA chromogranin A, *MIBG* Iodine-131-meta-iodobenzylguanidine, *5-HIAA* 5-hydroxyindoleacetic acid, *EUS* endoscopic ultrasound, *C/A/P* chest/abdomen/pelvis

Pancreatic NETs (pNET)

Nonfunctional pNETs

Workup	Surgical treatment [12–15]	Perioperative management	Follow-up (F/U)
• Labs: – CgA – Assess for functional tumor (see below) • Imaging: – Multiphase CT or MRI pancreas – Octreotide scan – EUS: consider for localizing small intrapancreatic lesions	• < 2 cm: – Observation versus surgical resection (enucleation or parenchymal sparing) should be offered and discussed with patient (no data to date supporting survival benefit with resection) – Considerations for location of small tumor (head versus tail of the pancreas) • > 2 cm: – Surgical resection; local resection when possible but consider multivisceral resection for locally advanced	• Insufficient data to recommend adjuvant therapy in completely resected locoregional disease	• < 1 year (every 3–6 mo) – CgA – CT C/A/P or pancreas MRI – If results are abnormal, octreotide scan or MIBG scintiscan • 1 year (every 6–12 mo): – CgA – CT A/P or MRI

CgA chromogranin A, *MIBG* Iodine-131-meta-iodobenzylguanidine, *5-HIAA* 5-hydroxyindoleacetic acid, EUS endoscopic ultrasound

Functional pNETs

	Clinical presentation	Workup	Surgical management [11–14]	Follow-up (F/U)
Insulinoma	• Whipple's Triad: – Hypoglycemia – Low blood glucose (<4 ng/ml) – Relief of symptoms with administration of glucose [13]	• Labs: – CgA – Insulin level – C peptide – Insulin antibodies – Blood glucose; supervised 48/72 h fasting glucose • Imaging: – Multiphase CT/MRI pancreas – Octreotide scan – EUS: consider for localizing small intrapancreatic lesions (90 % sensitivity) [13, 16]	• Enucleation – Tumors < 2 cm – Any located in the head of the pancreas • Local resections are preferred; avoid pancreaticoduodenectomy if possible • Considerations: – Laparoscopic approach if technically feasible – Intraoperative U/S: blind resection should be avoided	• Benign insulinomas do not require long term F/U. – Routine surveillance has not been shown to reduce the incidence of relapsing insulinomas [6] • Malignant: – Same as nonfunctional
Gastrinoma	• Ulceration/dyspepsia • Diarrhea (may resolve with PPI) • Multiple ulcers [13]	• Labs: – CgA – Gastric pH – Fasting serum gastrin: • > 1000 pg/ml: diagnostic of ZES • < 1000 pg/ml: order secretin or calcium stimulated gastrin • Imaging: – Upper endoscopy – Multiphase CT/MRI pancreas and abdomen – Octreotide scan	• Surgical resection decreases the risk of developing of metastases, improves survival • Consider local resection or enucleation for tumors < 2 cm where possible • Hypergastrinemia can be managed with PPIs [17]	• Malignant: – Same as nonfunctional

(continued)

(continued)

	Clinical presentation	Workup	Surgical management [11–14]	Follow-up (F/U)
Glucagonoma Somatostatinoma	• "Sweet" syndrome: – 4Ds: – Dermatosis (necrolytic migratory erythema) – Depression – Deep venous thrombosis – Diabetes: 40–90 % will have glucose intolerance, 70–90 % will sport characteristic rash [13]	• Labs: – CgA – **Serum Glucagon 500–1000 pg/ml (normal=<50)** • Imaging: – Upper endoscopy – Multiphase CT/MRI pancreas and abdomen – Octreotide scan	• Surgical resection + Lymphadenectomy • Aggressive resection in highly selected patients	• Malignant: – Same as nonfunctional
VIPoma	• Secretory diarrhea that persists with fasting • Possible steatorrhea (secondary to somatostatin inhibition of digestive enzymes) • Gallbladder disease • Hypochlorhydia • May arise in the pancreas, intestine or extrapancreatic sites [13]	• Labs: – CgA – **Elevated plasma somatostatin** • Imaging: – Upper endoscopy – Multiphase CT/MRI pancreas and abdomen – Octreotide scan	• Surgical resection + Lymphadenectomy • Aggressive resection in highly selected patients	• Malignant: – Same as nonfunctional

	• Watery, secretory diarrhea (>700 ml/day) • Hypokalemia • Hyperchlorydia • Acidosis [13]	• Labs: – CgA – **Elevated plasma vasoactive intestinal peptide** • Imaging: – Upper endoscopy – Multiphase CT/MRI pancreas and abdomen – Octreotide scan	• Surgical resection + Lymphadenectomy • Aggressive resection in highly selected patients	• Malignant: – Same as nonfunctional

CgA Chromogranin A, *EUS* endoscopic ultrasound, *PPI* proton-pump inhibitors

Special Notes

- Biopsy of nonfunctional tumors using endoscopic ultrasound (EUS) can be helpful in the presence of a nonspecific diagnosis and liver metastases, to rule out adenocarcinoma or in cases where tissue diagnosis is necessary to proceed with further treatment.
- Perioperative management:
  - Control of symptoms related to specific functional pNET
- Special Cases: Hereditary [12, 13, 15]
  - MEN-1:

    80–100 % will develop nonfunctioning pNETs
    0–13 % of pNETs will cause symptoms [14]
    54 % will develop gastrinomas (>80 % duodenal), most are multiple; 18 % insulinoma, <5 % glucagonomas, VIPomas, somatostatinomas
    Controversial: multiple, extensive resection is often necessary to remove all of the tumor for possibility of cure. Only 13 % of MEN-1 patients with nonfunctioning pNETs will grow larger or become symptomatic. The remaining 87 % will have a good prognosis without surgery [13]. Surgical treatment is not usually indicated.
  - VHL:

    10–17 % will develop a pNET, 98 % are nonfunctioning PNETs
  - NF-1 (von Recklinghausen):

    0–10 % will develop a pNET, usually duodenal somatostatinoma not associated symptoms
    During workup, endoscopic ultrasound can be helpful in identifying small lesions associated with hereditary conditions.

Workup

The workup of NETs can be divided into:

1. Functional status
   (a) Determine hormonal secretion
   (b) Evaluate clinical functional syndromes and their repercussions
2. Aggressivity and extent of disease
   (a) Imaging: CT C/A/P
   (b) Functional imaging: octreotide scan will be positive for well-differentiated NETs (G1/G2), FDG-PET will be positive for high grade NETs (G3) [18].
   (c) Biopsy to determine grade (Ki67 or MR)

Medical Management

Systemic therapy: Somatostatin analogs

- Somatostatin analogs play two roles in medical management of NETs: (1) symptom control and (2) antiproliferative effect.
- Antiproliferative effect (prolonged progression free survival) of long-acting forms has been proven in randomized controlled trials for well-differentiated enteric and pancreatic NETs (PROMID trial, CLARINET trial).
- Long-acting agents can be used alone or in combination with surgery in case of residual disease, for recurrent disease, or metastatic disease.

Systemic therapy: chemotherapy

- Well-differentiated NETs are traditionally resistant to chemotherapy agents, due to slow proliferation.
- Capecitabine–temozolomide can be used in selected cases of well-differentiated NETs. It has shown promising results in phase II studies, and is currently being investigated further.
- For high grade (G3) NETs, chemotherapy is the mainstay of treatment. Cisplatin–etoposide is the regimen of choice.

Systemic therapy: biologic agents

- Indicated for metastatic or progressing PNETs.
- Everolimus and Sutent have been associated with improved progression-free survival and overall survival.
- No evidence is currently available regarding their efficacy in gastroenteric NETs. This is currently investigated (e.g., RADIANT-4 trial).

Perioperative anesthetic management

- In patients with elevated urinary 5HIAA and/or carcinoid syndrome
  - Obtain a preoperative echocardiogram to rule out carcinoid heart disease prior to general anesthetic
  - Plan for perioperative octreotide administration to control serotonin secretion and reduce the risk of carcinoid crisis

Perioperative octreotide protocol

Patients well controlled on long-acting somatostatin analog (20 mg–30 mg IM)	• Additional dose of Octreotide LAR 60 mg 2–3 weeks prior to procedure • Supplementary dose of Octreotide IR 250 mcg–500 mcg SC 1–2 h before procedure • Carcinoid crisis with hypotension: – Fluid resuscitation – Intraoperative Octreotide 500 mcg–1000 mcg IV q5 min, may require infusion 50 mcg–200 mcg/h • Patients who have required supplemental doses intraoperatively should have 50 mcg–200 mcg/h infusion for 4–24 h postoperatively

(continued)

(continued)

Patients poorly controlled on long-acting somatostatin analog	• Additional dose of Octreotide LAR 60 mg 2–3 weeks prior to procedure • Supplementary dose of Octreotide IR 500 mcg–1000 mcg SC 1–2 h before procedure • Infusion of 100 mcg–250 mcg/h starting 1 h before procedure, continue 12–24 h after surgery, wean as tolerated
Patients not on therapy or for emergency Surgery	• 500 mcg–1000 mcg SC 1–2 h before procedure • Consider post-operative infusion 100 mcg–250 mcg/h

Adapted from: Belo S, Department of Anesthesia. Protocol for Perioperative Management of Patients with Carcinoid Syndrome. Sunnybrook Heath Sciences Centre. University of Toronto. 2011

Management of unresectable/metastatic functional/Nonfunctional pNETs (sporadic) [12–15]

Clinical scenario	Workup	Management	Follow-up (F/U)
Unresectable	• Labs: – Investigations based on clinical presentation as displayed above • Imaging: – Multiphase CT/MRI pancreas and abdomen – Octreotide scan to delineate primary tumor and extent of metastases – Further liver imaging (US/MRI/CT) as needed • Echocardiogram to rule out carcinoid heart disease	• Long-acting somatostatin analogs • Consider ablative therapies • Biological agents for PNETs • Peptide Receptor Radiotherapy (PPRT) • Functional: consider short-acting somatostatin analogs if symptoms not controlled with long-acting.	• Every 3–6 months: • CgA • 24 h urine 5-HIAA • CT A/P • Imaging should be tailored to management plan as determined by patient symptoms
Metastatic		• Consider liver debulking • Consider ablative therapies (HAE/TACE/RFA) • Liver transplantation in highly selected patients (potential candidates: young patients, metastatic disease isolated to liver, Ki-67 < 5 %, symptomatic). • Biological target agents for PNETs (Sutent, Everolimus) • Chemotherapy: consider capecitabine–temozolomide (phase II evidence only). • Primary tumor: if enteric localization—consider resection for symptom prevention and survival benefit [19].	

CgA chromogranin A, *5-HIAA* 5-hydroxyindoleacetic acid, *HAE*, hepatic artery embolization, *TACE* transarterial chemoembolization, *RFA* radiofrequency ablation

Special Notes

- Consider cholecystectomy at the time of surgery for any patient potential long-term use of somatostatin analogs or eventual need for right-sided liver embolization (TACE, HAE).
- Liver debulking:

  Considered to reduce tumor burden for symptom control and potentially improved efficacy of antiproliferative effects of long-acting somatostatin analogs.

  Recurrence is expected (>90 %), even after R0 resection [20].

  It can be combined with postoperative ablative therapies (HAE/TACE). No evidence is currently available on the benefits of multimodal therapy for metastatic NETs.

Relevant Publications on the Management of GEP NETs

Study	Methods	Results
PROMID [21]	• **Octreotide LAR** 30 mg vs. Placebo • Newly diagnosed, treatment-naïve patients with well-differentiated (G1) midgut NETs (both functional and nonfunctional) • Phase 3 • Primary end point: TTP	• Median TTP 14.3 vs. 6 months ($p < 0.001$) • Reduction of disease progression 66 %
CLARINET [22]	• **Lanreotide** vs. Placebo • Metastatic or unresectable, G1 or G2, midgut or hindgut NETs • Phase 3 • $N=204$ • Primary end point: PFS	• Median PFS 18.0 vs median not reached ($p<0.001$) • 24 months PFS 65.1 % vs 33.0 % • No difference in OS
RADIANT-3 [23]	• **Everolimus** (m-TOR inhibitor) vs. Placebo • Metastatic or unresectable pancreatic[a] NETs with radiologic progression • Phase 3 • $N=410$ • Primary end point: PFS	• Median PFS 11 vs. 4.6 months ($p < 0.001$) • Grade 3 or 4 drug-related adverse events 5 %
Sutent Trial [24]	• **Sunitinib** (tyrosine kinase inhibitor) vs. Placebo • Well differentiated metastatic or unresectable pancreatic[a] NETs and no candidates for surgery • Phase 3 • $N=171$ • Primary end point: PFS	• Median PFS 11.4 vs. 5.5 months ($p < 0.001$) • Improved OS (HR 0.42; $p=0.02$) • ORR 9.3 % ($p=0.007$)
CAPTEM [25]	• **Capecitabine–Temozolomide** as first line in metastatic well to moderately differentiated pancreatic[a] NET • Retrospective • $N=30$ • Primary end point: ORR	• ORR: 70 % • Median PFS: 18 months

[a]RADIANT-3, Sutent, and CAPTEM results are applicable only for PNETs; *PFS* progression free survival, *TTP* time to tumor progression, *ORR* objective response rate, *OS* overall survival

Referring to Medical Oncology

1. All NETs, particularly functional, should ideally be managed in conjunction with medical oncology and/or endocrinology as per individual institution [26].
2. Metastatic disease
3. Inoperable pNETs
4. Any poorly differentiated NETs
5. Patients with elevated 5-HIAA or carcinoid syndrome preoperatively
6. Patients with carcinoid syndrome requiring somatostatin analogs for symptom control
7. Candidates for clinical trials

Referring to Radiation Oncology/Interventional Radiology

1. Unresectable and metastatic tumors should be referred for discussion of new radioablative and ablative therapies.

Referring to Multidisciplinary Cancer Conference (MCC)

1. All neuroendocrine tumors would benefit from discussion and collaboration with MCC, and ideally, due to their rarity, would be best managed in a conjoint surgical/medical clinic [26].

Toronto Pearls

- Pathology interpretation is crucial to the proper identificationof neuroendocrine tumors.
- NETs profile can change over the course of disease, or from one site to another. Repeat biopsies can be considered to better tailor treatment [27].
- Treatment of primary neuroendocrine tumors does require some experience in order to ensure that maximum, but not over-aggressive lymphadenectomies are done, particularly to intestinal NETs.
- Metastatic neuroendocrine tumors require multidisciplinary planning. There are many options and most can be combined, including surgery and selective embolizations. Sequencing of therapies will take place over several years [26].
- Protocol for embolization:
  - Give 100 mcg octreotide iv bolus prior to procedure in angiography holding area (100 mcg in 50 ml NS over 10 min).

  - Start continuous infusion of octreotide at 50 mcg/h (500 mcg in 100 ml NS, i.e., 10 ml/h) for duration of procedure.
  - After 6 h from the start of octreotide infusion, decrease rate to 5 ml/h.
  - Stop infusion after the bag is finished unless patient is clinically symptomatic (e.g., flushing, palpitations, alteration of mental status, diarrhea, wheezing) or vital signs are abnormal.

- Use of radiotherapy options is starting to come into play; however, the delivery of peptide receptor radiotherapy requires the use of up-to-date agents, an experienced team, and careful dosimetry.
- Surgical therapy of neuroendocrine liver metastases is very different from the strategies used for other cancers, and parenchymal preservation is a very important principle of treatment. Anatomical liver resections should be avoided [28].
- Reevaluation of treatment options at each visit.
- Rising biochemical levels (i.e., CgA) often precede radiological change. Consider cross-sectional imaging and octreotide scan if CgA serum levels remain persistently elevated during surveillance.
- Reduction in biochemical levels (CgA and 5HIAA) during treatment is correlated with positive prognosis.

References

1. Yao JC, Hassan M, Phan A, et al. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. J Clin Oncol. 2008;26:3063–72.
2. Hallet J, Law CH, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: a population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015;121(4):589–97. PubMed.
3. Kloppel G, Perren A, Heitz P. U. (2004). The gastroenteropancreatic neuroendocrine cell system and its tumors: the WHO classification. Ann N Y Acad Sci. 2004;1014:13–27.
4. Bosman F, Carneiro F, Hruban R, Theise N, editors. WHO classification of tumors of the digestive system. Lyon, France: IARC Press; 2010.
5. Rindi G, Kloppel G, Ahlmann H, et al. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. Virchows Arch. 2006;449:395–401.
6. Boudreaux JP, Klimstra DS, Hassan MM, et al. The NANETS consensus guideline for the diagnosis and management of neuroendocrine tumors: well-differentiated neuroendocrine tumors of the jejunum, ileum, appendix, and cecum. Pancreas. 2010;39:753–66.
7. American Joint Committee on Cancer. AJCC cancer staging manual. 7th ed. New York, NY: Springer; 2010.
8. Klimstra DS, et al. Pathology reporting of neuroendocrine tumors: application of the Delphic consensus process to the development of a minimum pathology data set. Am J Surg Pathol. 2010;34(3):300–13.
9. Fendrich V, Waldmann J, Bartsch DK, et al. Multiple primary malignancies in patients with sporadic pancreatic endocrine tumors. J Surg Oncol. 2008;97:592–5.
10. Niederle MB, Niederle B. Diagnosis and treatment of gastroenteropancreatic neuroendocrine tumors: current data on a prospectively collected, retrospectively analyzed clinical multicenter investigation. Oncologist. 2011;16:602–13.

11. Sharpe SM, In H, Winchester DJ, Talamonti M, Baker MS. Surgical resection provides an overall survival benefit for patients with small pancreatic neuroendocrine tumors. J Gastrointest Surg. 2015;19:117–23.
12. Falconi M, Plockinger U, Kwekkeboom D, et al. Well-differentiated pancreatic non-functioning tumors/carcinoma: ENETS guidelines. Neuroendocrinology. 2006;84:196–211.
13. Kulke M, Anthony L, Bushnell D, et al. NANETS treatment guidelines: well-differentiated neuroendocrine tumors of the stomach and pancreas. Pancreas. 2010;39:735–52.
14. de Herder W, Niederle B, Scoazec J, et al. Well-differentiated pancreatic tumor/carcinoma: insulinoma. Neuroendocrinology. 2006;84:183–8.
15. Jensen R, Niederle B, Mitry E, et al. Gastrinoma (Duodenal and Pancreatic). Neuroendocrinology. 2006;84:173–82.
16. Vinik A, Woltering E, Warner R, et al. NANETS consensus guidelines for the diagnosis of neuroendocrine tumor. Pancreas. 2010;39:713–34.
17. Arnold R, Chen Y, Costa F, et al. ENETS Consensus guidelines for the standards of care in neuroendocrine tumors: follow-up and documentation. Neuroendocrinology. 2009;90:227–33.
18. Squires 3rd MH, Volkan Adsay N, Schuster DM, Russell MC, Cardona K, Delman KA, et al. Octreoscan versus FDG-PET for neuroendocrine tumor staging: a biological approach. Ann Surg Oncol. 2015;19. PubMed.
19. Hellman P, Lundstrom T, Ohrvall U, Eriksson B, Skogseid B, Oberg K, et al. Effect of surgery on the outcome of midgut carcinoid disease with lymph node and liver metastases. World J Surg. 2002;26(8):991–7. PubMed.
20. Sarmiento JM, Heywood G, Rubin J, Ilstrup DM, Nagorney DM, Que FG. Surgical treatment of neuroendocrine metastases to the liver: a plea for resection to increase survival. J Am Coll Surg. 2003;197(1):29–37. PubMed.
21. Rinke A, Müller HH, Schade-Brittinger C, et al. Placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors: a report from the promid Study Group. J Clin Oncol. 2009;27:4656–63.
22. Caplin ME, Pavel M, Cwikla JB, Phan AT, Raderer M, Sedlackova E, et al. Lanreotide in metastatic enteropancreatic neuroendocrine tumors. N Engl J Med. 2014;371(3):224–33. PubMed.
23. Yao JC, Shah MH, Ito T, et al. RAD001 in advanced neuroendocrine tumors, third trial (RADIANT-3) study group. Everolimus for advanced pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:514–23.
24. Raymond E, Dahan L, Raoul J-L, et al. Sunitinib malate for the treatment of pancreatic neuroendocrine tumors. N Engl J Med. 2011;364:501–13.
25. Strosberg JR, Fine RL, Choi J, Nasir A, Coppola D, Chen DT, et al. First-line chemotherapy with capecitabine and temozolomide in patients with metastatic pancreatic endocrine carcinomas. Cancer. 2011;117(2):268–75. PubMed.
26. Singh S, Law C. Multidisciplinary reference centers: the care of neuroendocrine tumors. J Oncol Pract. 2010;6(6):e11–6. PubMed Pubmed Central PMCID: 2988672.
27. Singh S, Hallet J, Rowsell C, Law CH. Variability of Ki67 labeling index in multiple neuroendocrine tumors specimens over the course of the disease. Eur J Surg Oncol. 2014;40(11):1517–22. PubMed.
28. Nadler A, Cukier M, Milot L, Singh S, Law CH. Hepatic parenchymal preserving technique in the management of diffuse bilateral neuroendocrine tumour liver metastases: a feasible approach. Can J Surg. 2014;57(2):E2–8. PubMed Pubmed Central PMCID: 3968200.

Chapter 17
Non-melanoma Skin Cancer

Jennifer Racz, Anthony M. Joshua, Joan E. Lipa, Alexander Sun, and Frances C. Wright

Introduction

Non-melanoma skin cancers (NMSC) are the most commonly diagnosed cancers in Canadians. In 2014, the Canadian Cancer Society estimated that there will be approximately 76,100 new cases and 440 deaths from squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) combined [1]. Although BCC is approximately four to five times more common (80 % of non-melanoma skin cancers) than SCC (20 % of non-melanoma skin cancers), the incidence of both tumor types continues to rise despite growing awareness of the risk factors [2]. BCC is characterized by local and sometimes disfiguring invasiveness; however, metastasis is rare,

J. Racz, M.D., M.B.A., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: jennifer.racz@gmail.com

A.M. Joshua, M.B.B.S., Ph.D., F.R.A.C.P.
Department of Medical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Anthony.joshua@uhn.ca

J.E. Lipa, M.D., M.Sc., F.R.C.S.C., F.A.C.S. • F.C. Wright, M.D., M.Ed., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: joan.lipa@sunnybrook.ca; frances.wright@sunnybrook.ca

A. Sun, M.D., F.R.C.P.C.
Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Alex.Sun@rmp.uhn.on.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_17

occurring in less than 0.05 % of cases [3]. SCCs, in contrast, are responsible for the majority of deaths from non-melanoma skin cancers as they have a higher metastatic potential (~5 % at 5 years). The American Joint Committee on Cancer (AJCC) 7th edition is the current recommended cutaneous squamous cell carcinoma and other cutaneous carcinoma staging system [4].

Risk Factors [5–10]

Risk factor	BCC	SCC
Exposure to ultraviolet light	Intense, intermittent exposure	Cumulative exposure
Increasing age	++	++
Fair complexion	++	++
Recreational tanning/tanning beds	++	++
Immunosuppression	++	++++
HPV		++
Exposure to ionizing radiation	++	++
Chemical exposure (i.e., arsenic, soot, tobacco, etc.)		++
Chronic inflammation		++
Personal history of skin cancer	++	++
Family history of skin cancer	++	++
Genetic syndromes • Xeroderma pigmentosum • Albinism • Muir–Torre syndrome • Fanconi anemia	++	++
Nevoid basal cell syndrome	++	

BCC basal cell carcinoma, *SCC* squamous cell carcinoma

Management: Primary Localized Basal and Squamous Cell Carcinoma (No Evidence of Regional or Metastatic Disease) [11]

Definition: Low- and High-Risk Factors for Local Recurrence of BCC [8, 11–20]

Risk factor	Low risk	High risk
Location and transverse size (i.e., diameter)	Site L—<20 mm Site M—<10 mm Site H—<6 mm	Site L—≥20 mm Site M—≥10 mm Site H—≥6 mm
Borders	Well defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	Negative	Positive
Site of prior radiation therapy	Negative	Positive
Subtype[a]	Nodular, superficial	Aggressive growth pattern[b]
Perineural involvement	Negative	Positive

Site L = trunk or extremity location
Site M = cheek, forehead, scalp, neck, or pretibial location
Site H = mask area of face, genitalia, hand, or foot location
[a]Low-risk subtypes include nodular, superficial, and other non-aggressive growth patterns such as keratotic, infundibulocystic, and fibroepithelioma of Pinkus
[b]Having morpheaform, basosquamous (metatypical), sclerosing, mixed infiltrative, or micronodular features in any portion of the tumor

Definition: Low- and High-Risk Factors for Local Recurrence or Metastases for SCC [8, 11–20]

Risk factor	Low risk	High risk
Location and transverse size	Site L—<20 mm Site M—<10 mm Site H—<6 mm	Site L—≥20 mm Site M—≥10 mm Site H—≥6 mm
Borders	Well defined	Poorly defined
Primary vs. recurrent	Primary	Recurrent
Immunosuppression	Negative	Positive
Site of prior radiation therapy or chronic inflammation	Negative	Positive
Rapid growth rate	Negative	Positive
Neurologic symptoms	Negative	Positive
Degree of differentiation	Well or moderate	Poor
Adenoid, adenosquamous, or desmoplastic subtypes	Negative	Positive
Depth (thickness or Clark level)	<2 mm or Clark I, II, or III	≥2 mm or Clark IV or V
Perineural or vascular involvement	Negative	Positive

Site L = trunk or extremity location
Site M = cheek, forehead, scalp, neck, or pretibial location
Site H = mask area of face, genitalia, hand, or foot location

Management of Low-Risk *Basal Cell Carcinoma and Squamous Cell Carcinoma*

Workup	Surgical techniques	Destructive techniques	Nonsurgical options	Follow-up
• History and physical examination • Complete skin examination • Assessment of regional nodal basins (SCC only) • No labs • No Imaging studies[a] • Biopsy[b]	• Wide local excision with post-operative margin assessment (POMA) (***4 mm*** margins for BCC and ***4–6 mm*** margins for SCC)[c]	• Curettage + electro-desiccation • Cryotherapy[d]	• Radiation therapy[e] • 5 % fluorouracil[e] • Imiquimod (Aldara®)[e] • Photodynamic Therapy (PDT)[e]	• History and physical with skin examination every 3–12 months for 2 years, then every 6–12 months for 3 years, then annually (SCC); [dermatologist] • History and physical with skin examination every 6–12 months for life (BCC) • Sun protection education

[a]Unless there is suspicion of deep structural involvement (i.e., bone, perineural disease, deep soft tissue or lymphovascular invasion); if perineural disease is suspected, MRI is preferred

[b]Punch or excisional biopsy techniques are preferred as the full thickness of the dermis can be evaluated; incisional biopsy is an option for large lesions, lesions in difficult locations or if an excisional biopsy would be cosmetically disfiguring

[c]Associated with 5-year disease-free survival of over 98 % for BCC and 92 % for SCC [21–23]

[d]Reserved for treatment of patients with low-risk, shallow NMSCs such as ***superficial BCC or SCC in situ*** (Bowen's disease)

[e]For patients unable or unwilling to undergo surgical treatment of primary lesions or when clear margins cannot be obtained by Mohs or more extensive surgery. Radiation should also be considered for primary treatment (instead of surgery) to sites where surgery may be disfiguring, cause significant morbidity, or require extensive reconstruction (i.e., nose, ears, eyelids, lips)

Management of High-Risk *Basal Cell Carcinoma and Squamous Cell Carcinoma*

Workup	Surgical techniques	Nonsurgical options	Follow-up
• History and physical examination • Complete skin examination • Assessment of regional nodal basins (SCC only) • No labs • No Imaging studies[a] • Biopsy • Multidisciplinary consultation (SCC only)	• Wide local excision with postoperative margin assessment (***6 mm*** margins for BCC and ***10 mm*** margins for SCC) • ***Mohs micrographic surgery*** (negative margins)[b] • Complete circumferential peripheral and deep margin assessment with frozen or permanent section (CCPDMA) • +/− SLNB (SCC only)—see next section	• Radiation therapy[c]	• History and physical with skin examination every 3–12 months for 2 years, then every 6–12 months for 3 years, then annually (SCC) • History and physical with skin examination every 6–12 months for life (BCC) • Sun protection education

SLNB sentinel lymph node biopsy

[a]Unless there is suspicion of deep structural involvement—fixed lesion/large lesion (i.e., bone, perineural disease, deep soft tissue); if perineural disease is suspected, MRI is preferred

[b]Associated with a 5-year disease-free survival rate of 99 % for BCC and 87 % for SCC [15, 24]; indications for Mohs procedure are centrofacially located tumors, large tumors, poorly defined tumor margins, recurrent lesions, lesions with perineural or perivascular involvement, tumors at a site of prior radiation therapy, tumors in the setting of immunosuppression, and patients with high-risk histological subtypes of BCC [6]

[c]For patients unable or unwilling to undergo surgical treatment of primary lesions or when clear margins cannot be obtained by Mohs or more extensive surgery; Radiation should also be considered for primary treatment (instead of surgery) to sites where surgery may be disfiguring, cause significant morbidity, or require extensive reconstruction (i.e., nose, ears, eyelids, lips). RTX should also be considered in the adjuvant setting if there is extensive perineural or large nerve involvement

Role for Sentinel Lymph Node Biopsy

- Although sentinel lymph node biopsy has been used in the management of select patients with high risk SCC, data are insufficient to determine whether early detection of microscopic metastatic disease has a beneficial effect on patient outcome. Thus, the procedure is not routinely recommended [25, 26].

Regional Metastatic Squamous Cell Carcinoma

Management of Regionally Metastatic *SCC [11]*

Work-up	Operable disease	Non-operable disease	Adjuvant treatment	Follow-up
• History and physical examination • Complete skin examination and assessment of regional nodal basins • Biopsy (FNA or core) of lymph node • Imaging studies for metastatic work up • MRI of head • CT chest, abdomen and pelvis • If locally advanced then use MRI to assess extent of muscle/bone/tendon involvement • Multidisciplinary consultation	• Wide local excision of primary lesion + regional lymph node dissection	• Radiation +/– concurrent chemotherapy followed by reassessment to determine eligibility for surgical resection	• Radiation therapy to regional lymph node basin[a]	• History and physical with complete skin and regional lymph node examination every 4–6 months for 3 years, then every 6–12 months up to 5 years • Sun protection education

[a]Consider for most head and neck primary lesions and for head and neck nodal basins or for trunk and extremity lesions that have lymph node basin involvement with multiple involved nodes or the presence of extracapsular extension

Referring to Medical Oncology

- All patients with distant metastases or locally advanced disease that cannot be adequately managed with surgical or radiotherapeutic techniques should be referred to medical oncology for consideration of systemic chemotherapy or clinical trial enrollment.
  - Vismodegib (BCC)
  - Cetuximab, Cisplatin/5-FU (SCC)
- Patients with borderline resectable disease (BCC) may also be considered for neoadjuvant Vismodegib

Referring to Radiation Oncology

- Patients should be referred to radiation oncology for consideration of radiation as primary therapy if:

  - they have histologically confirmed NMSCs and are unable or unwilling to undergo surgical treatment of their primary lesion;
  - clear margins cannot be obtained by Mohs or more extensive surgery;
  - surgery may be disfiguring, cause significant morbidity, or require extensive reconstruction (i.e., nose, ears, eyelids, lips).
- All patients with positive margins, regional or metastatic disease should also be referred to radiation oncology for consideration of adjuvant radiation therapy.

Referring to Multidisciplinary Cancer Conference

- Patients with positive deep margins following resection with graft/flap reconstruction
- All patients with regionally metastatic NMSCs
- All patients with distant metastatic NMSCs

Toronto Pearls

- Patients with high risk BCCs or SCCs on the face should be prepared for graft or local flap reconstruction given the cosmetically sensitive nature of this region; high risk SCCs in other locations may also require graft/flap reconstruction given the potential size of resection.
- If deep margins are positive following resection and reconstruction, consideration should be given to re-resection.
- Level 3 axillary dissection for SCC should be considered for palpable disease.

References

1. Canadian Cancer Society: Non-melanoma skin cancer statistics. Available at http://www.cancer.ca/en/cancer-information/cancer-type/skin-non-melanoma/statistics/?region=on.
2. Christenson LJ, Borrowman TA, Vachon CM, et al. Incidence of basal cell and squamous cell carcinomas in a population younger than 40 years. JAMA. 2005;294:681–90.
3. Ting PT, Kasper R, Arlette JP. Metastatic basal cell carcinoma: report of two cases and literature review. J Cutan Med Surg. 2005;9:10–5.
4. Edge SB, Byrd DR, Compton CC, et al. (eds). AJCC cancer staging manual: Cutaneous non-melanoma skin cancer. 7th Ed. New York, NY: Springer, 2010.
5. Chung S. Basal cell carcinoma. Arch Plast Surg. 2012;39:166–70.
6. Mortenson MM, Herne K, Hymes SR, Cormier JN. Nonmelanoma skin cancer. The MD Anderson Surgical Oncology Handbook 5th Edition. Philadelphia, PA: Lippincott Williams and Wilkins; 2012. p. 152–64.
7. Wong CSM, Strange RC, Lear JT. Basal cell carcinoma. BMJ. 2003;327:794–8.
8. Rubin AI, Chen EH, Ratner D. Basal-cell carcinoma. N Engl J Med. 2005;353:2262–9.

9. Perkins JL, Liu Y, Mitby PA, et al. Nonmelanoma skin cancer in survivors of childhood and adolescent cancer: a report from the childhood cancer survivor study. J Clin Oncol. 2005;23:3733–41.
10. Karagas MR, Nelson HH, Zens MS, et al. Squamous cell and basal cell carcinoma of the skin in relation to radiation therapy and potential modification of risk by sun exposure. Epidemiology. 2007;18:776–84.
11. NCCN practice guidelines in oncology: basal cell and squamous cell skin cancers. Version2, 2014 [online]. Available from URL: http://www.nccn.org/professionals/physician_gls/pdf/nmsc.pdf
12. Boeta-Angeles L, Bennett RG. Features associated with recurrence (basal cell carcinoma). In: Miller SJ, Maloney ME, editors. Cutaneous Oncology Pathophysiology, diagnosis, and management. Malden, MA: Blackwell Science; 1998. p. 646–56.
13. Haas AF. Features associated with metastasis (squamous cell carcinoma). In: Miller SJ, Maloney ME, editors. Cutaneous Oncology, Pathophysiology, diagnosis, and management. Malden, MA: Blackwell Science; 1998. p. 500–5.
14. Clayman GL, Lee JJ, Holsinger FC, et al. Mortality risk from squamous cell skin cancer. J Clin Oncol. 2005;23:759–65.
15. Rowe DE, Carroll RJ, Day Jr CL. Prognostic factors for local recurrence, metastasis, and survival rates in squamous cell carcinoma of the skin, ear, and lip. Implications for treatment modality selection. J Am Acad Dermatol. 1992;26:976–90.
16. Randle HW. Basal cell carcinoma. Identification and treatment of the high-risk patient. Dermatol Surg. 1996;22:255–61.
17. Rieger KE, Linos E, Egbert BM, Swetter SM. Recurrence rates associated with incompletely excised low-risk nonmelanoma skin cancer. J Cutan Pathol. 2010;37:59–67.
18. Rowe DE, Carroll RJ, Day Jr CL. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. J Dermatol Surg Oncol. 1989;15:315–28.
19. Ulrich C, Kanitakis J, Stockfleth E, Euvrard S. Skin cancer in organ transplant recipients-where do we stand today? Am J Transplant. 2008;8:2192–8.
20. Brantsch KD, Meisner C, Schonfisch B, et al. Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. Lancet Oncol. 2008;9:713–20.
21. Samarasinghe V, Madan V. Nonmelanoma skin cancer. J Cutan Aesthet Surg. 2012;5:3–10.
22. Brodland DG, Zitelli JA. Surgical margins for excision of primary cutaneous squamous cell carcinoma. J Am Acad Dermatol. 1992;27:241–8.
23. Wolf DJ, Zitelli JA. Surgical margins for basal cell carcinoma. Arch Dermatol. 1987;123:340–4.
24. Rowe DE, Carroll RJ, Day Jr CL. Mohs surgery is the treatment of choice for recurrence (previously treated) basal cell carcinoma. J Dermatol Surg Oncol. 1989;15:424–31.
25. Ross AS, Schmults CD. Sentinel lymph node biopsy in cutaneous squamous cell carcinoma: a systematic review of the English literature. Dermatol Surg. 2006;32:1309.
26. Renzi C, Caggiati A, Mannooranparampil TJ, et al. Sentinel lymph node biopsy for high risk cutaneous squamous cell carcinoma: case series and review of the literature. Eur J Surg Oncol. 2007;33:364.

Chapter 18
Palliative Surgical Care

Juan Camilo Correa, Alexandra M. Easson, Anand Govindarajan, and Lucy Kathryn Helyer

Introduction

According to the Canadian Cancer Society, 1 in 4 Canadians will die from cancer, which is the leading cause of premature death. Most cancer patients are cared for by surgeons along the trajectory of their illness, both in the early and terminal stages. The role of surgery, however, is poorly defined in the treatment of terminally ill patients and surgical oncologists report limited exposure to palliative care during their training [1].

The World Health Organization (WHO) defines palliative care as "the active total care of patients who are unresponsive to curative treatment [2]." When Balfour Mount, a Canadian urologist, coined the term "palliative care," his goal was to anticipate, prevent and relieve the suffering experience in patients during the late phase of their life-threatening condition or disease. Palliative care includes expertise in pain and non-pain symptom management, difficult communication such as giving bad news, discussing Do Not Resuscitate (DNR) orders and advance directives, early recognition of the need to discuss such issues, and an ability to develop a care plan with the patient and family that best fits the patients' goals of care. Given that the condition of the patient changes frequently, previously discussed advanced directives may change, and should be rediscussed if deemed appropriate.

J.C. Correa, M.D. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: jcccote@yahoo.com

A.M. Easson, M.D., M.Sc., F.R.C.S.C. • A. Govindarajan, M.D., M.Sc., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: Alexandra.Easson@uhn.ca; agovindarajan@mtsinai.on.ca

L.K. Helyer, M.D., M.Sc., C.C.F.P., F.R.C.S.C.
Department of Surgery, Queen Elizabeth II Health Sciences Centre, Halifax, NS
e-mail: lhelyer@dal.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_18

Though varying definitions exist, *palliative surgery* is a surgical procedure designed to improve quality of life, relieve or prevent symptoms caused by an advanced disease [3]. Up to 10–20 % of all surgical oncology procedures are palliative in nature [2]. *Palliative surgery* must be distinguished from *non-curative surgery*, where the primary intent is not the improvement of quality of life.

Palliative Surgery

Goals of Palliative Surgery

- Primary outcome: improvement in quality of life through the relief of symptoms caused by an advanced disease [4].
- Secondary outcome (but not goal of treatment): improvement in survival.
- Successful outcome defined by patient and surgeon preoperatively.
  - Relief from distressing symptoms, easing of pain, and improvement in quality of life.
  - May increase response to chemotherapy or radiotherapy in certain circumstances [5].
- The decision to intervene is based on the treatment's ability to meet these goals, rather than its effect on the underlying disease.

Surgical Decision-Making in the Advanced Cancer Patient

Identify	Assess	Discuss and recommend
• Symptoms: – Nausea/ vomiting – Anorexia – Abdominal cramping – Pain – Bleeding • Potential surgical causes: – Mechanical bowel obstruction – Bleeding site – Eroding tumor – Tumor bulk – Ascites	• Patient factors: – Prognosis—Multidisciplinary discussion – Age—biologic, physiologic – Concurrent illness and comorbidities – Malnutrition and/or cachexia – Performance status – Ascites • Technical factors: – Select degree of invasiveness of the intervention: Interventional radiology < endoscopy < laparoscopy < laparotomy – Anesthetic requirements – Risk of post-procedure complications	• Discuss with patient and family: – Does this procedure fit with the patient's goals of care? – What do they understand about their disease and where are they on their disease trajectory? – Determine whether symptom alleviation fits the goals of care of the patient. Explain clearly the expected potential benefits of any intervention: Is this something that would be worth it to them given the risks? – Provide a commitment to continue to care for the patient regardless of the outcome of the discussion • Formulate recommendation(s) – Consider all options – What is feasible? What is futile? – No ethical or legal obligation to offer futile treatment

(continued)

(continued)

Identify	Assess	Discuss and recommend
• When Deciding to Operate: – Thorough preoperative evaluation to avoid intraoperative surprises – Prevention of emergency situations – Communication with the patient and family about the goals of care, likelihood of success – Discuss all potential outcomes of the procedure – A commitment to ongoing care with a clear care plan, whatever outcome of surgery		

The first step for consideration of palliative surgery is proper patient selection. Patients with at least a 3-month expected survival may be considered adequate candidates [5].

Patient's choices are greatly influenced by the physician´s recommendations, being the predominant reason for treatment selection in up to 40 % of the cases; therefore the situation should be managed carefully, always trying to give the patient all the information they need to make a conscious decision [6]. When discussing treatment options and a possible surgical approach, the attending physician must choose his words wisely, making sure to explain the current status of the patient, the goals of treatment, its possible benefits and also the risks involved.

Postoperative care should also be an important issue discussed with patients. Routine postoperative care, the risks of developing complications, requiring additional actions (e.g., ICU, Mechanical Ventilation), the aggressiveness of treatments in the event of any postoperative complication, and the risk of spending an important part of their remaining lifespan in the hospital must be addressed [7, 8].

Examples of Indications for Palliative Surgical Procedures
• Drainage of Fluid: – Pleural effusions, ascites
• Relief of Obstruction: – GI tract from mouth to anus – GU tract from kidney to bladder neck
• Prevention of Bleeding: – Tumor resection – Ligation or embolization of feeding vessels – Radiation
• Palliative Tumor Resection: – Space occupying lesions in the cranium – Prevent/palliate bleeding, obstruction, fungation, neuropathic pain
• Fixation for bony metastases and impending fracture

Expected Survival

There are many tools available to determine the expected survival; it is important for the clinician and patient to have a rough estimate, so they can weigh the pros and cons of the treatments offered. In these settings early involvement of the palliative care specialists has shown multiple benefits [9].

The Clinical prediction of survival is a useful tool but should not be relied upon as the sole decision factor, because its performance varies with physician experience. There have been other clinical factors associated with a shorter life expectancy, such as low performance status, symptoms of cachexia-anorexia syndrome, delirium, and dyspnea [10].

A number of prognostic scores have been developed, such as the Palliative Prognostic Index (PIP), the Palliative Prognostic Score (PaP) and the PiPS-A and PiPS-B (*available at www.pips.sgul.ac.uk*) [10, 11]. Any of these scores can be used to determine the patient life expectancy and aid in the decision-making process.

Evaluation Outcomes

Currently, there are no validated instruments to measure Quality of Life (QOL) after palliative procedures. In the absence of a good measurement tool, the absence of a postoperative complication has been used as an indicator of QOL [2]. In the absence of a validated instrument, the Palliative Surgery Outcome Score (PSOS) has been used as a measure of symptom resolution after a palliative procedure.

$$\text{Palliative Surgery Outcome Score } (\text{PSOS}) = \text{SFD} / \text{POD}$$

SFD = Number of days a patient is without symptoms and not in the hospital. The symptoms refer to the ones that were meant to be treated, and include complications related to the surgical procedure.
POD = Number of total days of life after the operation (up to 180 days).

The PSOS score is an estimated measure of the impact of a palliative surgical procedure on patient wellbeing. A PSOS score >0.7 is considered to be an acceptable outcome score.

Specific Clinical Scenarios

Malignant Bowel Obstruction

Malignant bowel obstruction (MBO) is estimated to occur in 15 % of all palliative care patients and encompasses a heterogeneous clinical syndrome, defined as obstructive symptoms due to the presence of intra-abdominal neoplastic disease. The small bowel is more commonly involved than large bowel, and the most common causes are ovarian or colon cancer [2, 12–15]

MBO can be due to extraluminal compression, intraluminal obstruction or functional obstruction due to tumor infiltration of the mesentery, nerve involvement or paraneoplastic neuropathy [14]. Often, obstruction involving the small bowel is

multifocal (carcinomatosis), in contrast to large bowel obstruction which is usually endoluminal and unifocal (solitary tumor). The site and degree of involvement of the bowel determines the treatment path.

High-quality imaging is crucial to rule out signs of a surgical emergency and to properly characterize the obstruction (location, degree, multifocality, and cause). In addition, imaging can rule out other non-neoplastic causes of obstruction, which can be found in up to 15–30 % of patients with previously known peritoneal carcinomatosis [14].

Special Notes:

- Criteria for MBO:
  - Clinical evidence of bowel obstruction
  - Obstruction beyond the ligament of Treitz
  - Caused by incurable intra-abdominal cancer **or** extra-abdominal cancer with peritoneal disease
- Clinical variables associated with decreased survival in patients with MBO [8]:
  - ECOG status 2–4
  - Elevated BUN
  - Low albumin
  - Ascites
  - Palpable mass
  - Continued postoperative obstruction
- Careful patient selection is important, as operative morbidity and mortality are high.
- Most important prognosticator for survival in these patients is functional status
- Patients should also be aware of the risk of failure of the intent of surgery

Malignant bowel obstruction (MBO) management steps	
1. Fluid Resuscitation	
2. Nasogastric Decompression	• Should be reserved for the period of initial evaluation, for temporary relief, until more durable measures are initiated or resolution of the episode has occurred or as an adjunct to perioperative care.
3. Radiologic Investigations	• To determine: – Single site vs. multiple sites – Anatomic site, e.g., gastric outlet, small bowel, large bowel – Partial vs. complete obstruction – Amount of metastatic disease, presence of ascites, and assess the realistic ability of an intervention to relieve the symptoms

(continued)

(continued)

Malignant bowel obstruction (MBO) management steps		
4. Symptom Management	***Anti-secretory***	• Octreotide • Buscopan
	Antiemetic	• Haloperidol • Stemetil • Gravol • Dexamethasone
	Antispasmodic (colicky pain)	• Loperamide • Buscopan
	Analgesic	• Morphine/hydromorphone • Fentanyl patch
	Intravenous Hydration	• If no reversible cause found for MBO or if no appreciable change with steroids and Octreotide • Can be maintained via SC boluses if required • Controversial when to stop
5. Indications for Surgery	• Ischemic complications are rare → allows for careful patient selection for operative therapy • Risk of major surgical complications after surgery is 7–44 %. 30 day mortality ranges between 6 and 32 %[8, 15] • Obstructive symptoms resolution may vary between 32 and 100 %, re-obstruction occurs in 6–47 % [8] • Symptom relief may be short lived, with only 32–71 % being symptom free at 60 days postoperatively [8] • Surgery as a bridge to palliative chemotherapy is associated with prolonged survival over surgery alone	

MBO malignant bowel obstruction

Gastric Outlet Obstruction (GOO)

Most common causes are cancers of the stomach, pancreas, and periampullary/biliary tract, as well as lymphoma and metastases [16]. Treatment is necessary, as patients quickly develop vomiting, dehydration and malnutrition [17]. The goal of therapy is to restore the ability to tolerate diet orally.

	Treatment options [16, 18]
Gastrojejunostomy (GJ)	• Open vs. laparoscopic • More medical complications in early postoperative period • Consider for patients with longer anticipated survival • Better functional outcomes in the long term [19]
Endoscopic Stent	• Improved time to PO intake • Shorter hospital stay • Higher re-obstruction rate and late complications (20–44 %) • Consider for patients with shorter anticipated survival

(continued)

(continued)

	Treatment options [16, 18]
Gastrostomy with Tube Decompression	• May provide relief from intractable nausea • Placement via endoscopy, interventional radiology or surgically • Ideally should be placed into the posterior wall of the stomach

Patient selection for the appropriate therapy is important, because the outcome depends on the clinical condition of the patient and their anticipated lifespan. A WHO performance status >2 or short expected lifespan should prompt consideration for stent therapy, given the poor prognosis of this group of patients.

In patients with periampullary cancer who underwent a surgical exploration and were deemed unresectable, a prophylactic gastrojejunostomy should be considered (up to 20 % of these patients will develop GOO). A Cochrane review demonstrated no increased morbidity and compared to patients with no GJ their risk of developing GOO in the future was lower (2.5 % vs. 28 %) [20].

Large Bowel Obstruction (LBO)

80 % of all LBO are malignant in nature and up to 10–30 % of patients with colorectal cancer present with acute obstructive symptoms. Usually, it is associated with fluid and electrolyte disturbances [13].

Obstructive lesions are more commonly found in the left Colon, and in the acute obstructive setting they are associated with worse oncological outcomes and a higher incidence of local spread and metastatic disease [21].

	Treatment options [13, 21]
Surgical Resection and Anastomosis	• Option in patients with less advanced disease • May involve multistage resection with temporary stoma • Considered the ideal management for lesions proximal to the splenic flexure. Patient selection is advised. Anastomotic leak rates of 2.8–16.4 %[13] • Resolution of obstruction 98 %
Surgical Resection and Hartmann's	• Less complex procedure in the acute setting • Avoids the morbidity of an anastomosis. • Reconstruction of the Hartmann's is only attempted in 60 % of the patients. • Morbidity 5–57 %[13]
Surgical Diversion with Stoma	• High morbidity and mortality • Option in patients with mid or distal rectal tumors: – There is no strong evidence for stents in proximal colon or rectal tumors as definitive palliative management [22]. – Some patients derive benefit from neoadjuvant therapy. Initially unresectable liver metastasis may become resectable after chemotherapy in 12–26 % of the cases [23, 24].

(continued)

(continued)

	Treatment options [13, 21]
Colonic Stenting	• Effective with minimal morbidity • Definitive Therapy [22, 25]: – Technical success in 88 %. Clinical success (evidence of intestinal transit) up to 95 % – Median patency ranges between 55 and 343 days. – Less success in tumors close to anal verge (<5 cm) – Compared to surgery, stents had a shorter length of hospital stay, lower rates of ICU admission, lower 30-day mortality rates, lower rates of early complications (<30 days), and a shorter time to initiation of chemotherapy. The overall survival was the same, but there was a lower clinical success rate and higher rate of late (>30 days) complications [25]. – Complications: Perforation 10 %, Migration 9 %, and stent obstruction 18 % – Not recommended if angiogenesis inhibitor (e.g., Bevacizumab) chemotherapy is going to be administered, because the increased risk of perforation. • Bridging therapy to surgery: – Technical success in 70 %. Clinical success 52.5–78 % – Increases the possibility of a primary anastomosis and avoiding a stoma [13, 21, 26] – No difference in permanent stoma rates, 30 day mortality, surgical site infection, or anastomotic leakage [13, 21, 22, 26]

Biliary Duct Obstruction

Malignant bile duct obstruction can be due to intraluminal tumor presence, local invasion of primary disease, extraluminal compression, or metastatic cancers [27].

	Treatment options [28]
Surgical Diversion	• Options: Hepaticojejunostomy, Segment III cholangiojejunostomy, right sectoral duct bypass or transtumoral tube placement. • Considered in patients deemed unresectable during surgical exploration, or when endoscopic and/or percutaneous stenting has failed.
Endoscopic Stenting	• Option for patients with obstruction distal to the hilum. • Plastic stents (PS) have a patency time of 1.4–3 months. Self-expandable metal stents (SEMS) are patent for 6–10 months [28, 29]. • If life expectancy is greater than 4 months, SEMS are recommended [30]
Percutaneous Stenting [27]	• Option for patients with advanced disease, and proximal (common hepatic duct or higher) obstruction. • Success in 77–98 % of Interventions • Stent Occlusion 5–25 %

Malignant Ascites

The pathogenesis of Malignant Ascites (MA) is multifactorial. Increased production of peritoneal fluid due to high permeability of the tumor generated neovascularization, and diminished reabsorption (secondary in most cases to obstruction of fluid drainage through peritoneal "stomata") are the main causes [31, 32].

It is a sign of poor prognosis, median survivals range from 10 weeks in foregut tumors to 20 weeks in gynecological tumors.

	Treatment options [31, 33]
Diuretic Therapy [33]	• Successful in approximately 40 % of cases. • More useful in patients with liver metastasis and portal hypertension • Better results when combined with other therapies
Paracentesis	• Symptom resolution in 90 %. Need for repeated treatments. • Especially indicated in patients who need rapid resolution of symptoms. • Up to 5 L of fluid can be removed, without requiring IV fluid replacement. – No evidence of benefit from albumin replacement. Studies in MA have used D5W [33]
Permanent Catheters (Tunneled) [31, 34]	• Ideal for patients requiring frequent paracentesis (<7 days of interval) • Risk of peritonitis (1–4.4 %). Complications 7 %
Intraperitoneal Chemotherapy	• Range of success depends on tumor type. Ranges between 33 and 65 %
Cytoreductive Surgery (CRS) and Heated Intraperitoneal Chemotherapy (HIPEC) [35]	• Resolution of ascites in 93 % • Resolution of ascites not related to R0–R1 or R2 resection. • Magnitude of preoperative ascites did not correlate with the probability of resolution. However there was an inverse correlation between quantity of ascites and R0–R1 resection. • Survival advantage with R0–R1 resections • Not considered an ideal "palliative option"
Laparoscopic HIPEC [36, 37]	• Valuable option for patients not eligible for CRS + HIPEC. Considered a viable "Palliative therapy" • Resolution of ascites in 95 % of patients. • Mean Hospital Stay 2.3 days. • No Cytoreductive Surgery required

(continued)

(continued)

	Treatment options [31, 33]
Surgical Peritoneovenous Shunts [38]	• High rates of complications (up to 38 %). Occlusion 24 % • Shunt revision in 12 % • Use in extremely selected patients with life expectancy greater than 3 months • Contraindicated in patients with heart or renal failure, portal hypertension, loculated effusions, and haemorrhagic ascites • Prevents protein and fluid loses [33]. • Better outcomes in patients with non-gastrointestinal cancer • Median patency of peritoneovenous shunt (Denver®) is 3 months

Symptoms

Pain

Even though it has been recognized as the fifth vital sign and a lot of research has been done to improve its management, we have not risen to the challenge yet. Currently it is estimated that up to 60 % of patients with cancer have pain issues, and up to 75 % of the patients who are under treatment for cancer pain are under-treated [39, 40].

Pain Assessment [40, 41]

- Characterize its dimensions
  - Location, duration, radiation, temporal pattern, provocative or relieving factors)
- Formulate an understanding of the nature of the pain
  - Etiology (Cancer related, treatment related or not related to cancer)
  - Pain Mechanism
- Quality:
  - Somatic (dull/aching, well localized)
  - Visceral (dull/sharp/colicky, referred)
  - Neuropathic (burning, stabbing, itching, radicular)
- Impact of pain in activities of daily living
  - Emotional component: *What does it represent to the patient?*

- Severity:
  - 0 (no pain)-10(most severe possible)
- Clarify the extent of the neoplastic disease
- Elucidate comorbidities
  - Screen for alcohol and smoking dependencies
- Treatment:
  - What has been used to relieve the pain
  - Determine the need for other palliative care interventions
  - Identify barriers to treatment (patients' beliefs, physicians' misconceptions, fear of addiction to opioids)

A useful mnemonic is LMNOPQRST (location, medical treatments, number of episodes, onset, position, quality, radiation, severity, and triggers [41]).

There are multiple ways to treat cancer related pain, and a clinician should always recognize that pharmacological management is only one of them.

Categories of treatment for pain related to cancer	
Pharmacologic	• Opioids/Non-opioids/Adjuvant Analgesics
Intervention	• Implant/Injection Therapies • Neural Blockades
Radiation therapy	• Treatment of bone pain, malignant spinal cord compression or brain metastasis [42]
Rehabilitative	• Therapeutic Exercise • Occupational Therapy • Therapies for specific disorders (e.g., Lymphedema)
Psychological	• Psychoeducational interventions • Cognitive-behavioral therapy
Neurostimulation	• Transcutaneous • Transcranial
Integrative or Complementary	• Acupuncture • Massage

Adapted from Portenoy et al. and Auret et al. [40, 43]

Pharmacological Pain Management

- Degree of pain (mild/moderate/severe) determines selection of analgesic
- Oral route preferred, avoid IM route, IV route for quick onset (severe pain).
  - Subcutaneous route is reserved for advanced disease and management of dehydration.
- At appropriate doses, respiratory depression is uncommon with opioid use in palliative cancer patients
- Addiction is rare when pain is present

Pharmacological pain therapies		
Mild Pain	Moderate pain	Severe pain
• Acetaminophen or NSAID (aspirin or ibuprofen)	• Single agents: – Codeine 5–10 % of patients may be slow CYP2D6 metabolizers and experience no benefit from codeine. – Oxycodone • Combination: – Acetaminophen with codeine	• First line drug is morphine—Use hydromorphone in elderly or renal impaired • Start with routine q4h doses of immediate release until pain control achieved. Do not start sustained release until pain control stable for a few days • Breakthrough (PRN) doses should also be prescribed • Monitor and titrate frequently, change q4h dose when you know how much was needed in 24 h, watch for over-sedation and respiratory depression • Always prescribe a laxative and antiemetic with opiates • 30 mg oral morphine = 20–30 mg oral oxycodone=7.5 mg oral hydromorphone=10 mg IV/SC morphine=2 mg IV/SC hydromorphone • Conversion is an estimate so use 50–75 % of new dose to avoid overdosing • FENTANYL patch (mcg) = 24 h oral morphine dose/2. Round down to avoid overdosing.

Special Notes

- If there is a decline or fluctuation in renal function, the use of an opioid without active metabolites, such as fentanyl, or with a lower concentration of renally cleared metabolites, such as hydromorphone, is recommended [40].
- Opioid rotation: A change from one opioid to another, in patients who are poorly responsive to an initial medication is accompanied by a better therapeutic outcome. Response is evident in approximately 2/3 of the patients who are switched [40].

Adjuvant Analgesics

Especially useful in cancer related neuropathic pain [43]. The number needed to treat (NNT) to prevent one episode of pain for many adjuvant drugs is 3–5 [44], and drug toxicity is limiting. The overall clinical picture of the patient, and possible secondary benefits (e.g., treatment of concomitant depression) should guide agent selection.

Class	Notes	Examples
Antidepressants	• Start low dose • Escalate slowly (2–3 days) • DC if no effect in 1 week	• Amytriptyline • Venlafaxine • Duloxetine
Anticonvulsants	–	• Gabapentin • Pregabalin • Carbamazepine
Corticosteroids	• Limited for long-term use	• Dexamethasone • Prednisone
Bisphosphonates	• Bone pain from metastases in normocalcemic patients • 14–28 days for effect	• Pamidronate • Zolendronate • Denosumab

Adapted from: Dunn et al. 2009 [2] and Auret et al. [43]

Nausea

20–30 % of people with advanced cancer suffer from nausea, and the effect on their quality of life can be devastating [45]. There are different mechanisms that can cause nausea in palliative cancer patients; it is important to try to determine the cause so the treatment can be tailored to it.

Causes of Nausea in the Cancer Patient [2, 45]	
Pharmacologic	• Opioids/Non-opioids/Adjuvant Analgesics – In patients with reversible causes for nausea, it may be the culprit in up to 50 % – If related to opioids, a dose reduction or opioid rotation may reduce the severity [45]
Elevated Intracranial Pressure	• Metastatic/primary brain lesions • Blockage of cerebrospinal fluid collecting system • Leptomeningeal disease
Vestibular	• Stimulation of vestibular system
Emotional/Psychological	• Anticipatory nausea prior to chemotherapy or procedures • Anxiety
Gastrointestinal	• Impaired gastric motility • Constipation • Obstruction
Metabolic Causes	• Electrolyte disorders

Nondrug Therapy for Nausea and Vomiting [46]

- Cool cloth, fan
- Bland, room temperature foods, limit fluids with foods
- Decrease: stimuli
- Acupuncture or acupressure

Pharmacologic Management for Nausea and Vomiting [46]

Class	Indications	Examples
Serotonin agonist	• Stimulation of Chemoreceptor trigger zone (CTZ): ex morphine, hypercalcemia, uremia	• Ondansetron
Dopamine agonist	• Stimulation of CTZ	• Haloperidol
Promotility	• Gastric stasis (should be avoided in patients with query obstruction)	• Metoclopramide
Glucocorticoids	• Consider in patients with elevated ICP	• Dexamethasone
Antihistamine	• Vestibular nausea (movement related, tumor, infections, morphine)	• Diphenhydramine
Benzodiazepines	• Helps prevent anticipatory nausea and vomiting (limbic system)	• Lorazepam

ICP intracranial pressure

Dyspnea

Dyspnea is the subjective sensation of uncomfortable breathing that may not relate to measured oxygen saturation or blood gases. It is strongly associated with anxiety (feedback loop).

Nondrug Therapy

- Positioning
- Supplemental oxygen (preferably nasal cannula) titrated to symptom relief not pulse oximetry
- Increase air movement (fans)
- Humidified air
- Behavioral treatment

Drug therapy [2]

Symptoms	Class	Examples
• Cough	• Opioid • Inhaled local anesthetics may be used for cough, though impairs gag reflex and limits ability to taste	• Dextromethorphan, codeine • Inhalated lidocaine
• Patients with air hunger	• Opioids	• Morphine
• Patients experiencing anxiety, panic or sense of suffocation	• Anxiolytics	• Lorazepam • Diazepam
• Bronchospasm • Superior Vena Cava Syndrome • Parenchymal metastases	• Corticosteroids	• Dexamethasone • Prednisone

(continued)

(continued)

Symptoms	Class	Examples
• Excessive watery secretions	• Anticholinergic	• Glycopyrrolate
• Excessive thick secretions	• Sedatives • Avoid anticholinergics (causes increased thickening of secretions) • Avoid suctioning if possible, (causes patient distress [46])	• Chlorpromazine

Constipation

Very common symptom in patients with cancer, its prevalence can be between 70 and 100 % [47]. In every patient with new onset constipation, or a change from his regular bowel habits other diseases must be ruled out, especially obstruction [2, 47].

- Prevention is more effective than cure. Considerations include addition of stool softeners or laxatives when ordering opioids (constipation is the most frequent and persistent side effects of opioid therapy [47])
- Stool softeners or bulking agents alone may not be adequate

	Treatment options [47]
First line	• Sennekot +/− milk of magnesia
Second line	• Bisacodyl
Third line	• Fleet enema • GoLYTELY enema • Lactulose • Methylnaltrexone IV or SC
Fourth line	• Magnesium citrate, repeat enema, manual disimpaction

References

1. McCahill LE, Krouse R, Chu D, Juarez G, Uman GC, Ferrell B, et al. Indications and use of palliative surgery-results of Society of Surgical Oncology survey. Ann Surg Oncol. 2002;9(1):104–12.
2. Dunn G, Martensen R, Weissman D. Surgical palliative care: a residents guide. American College of Surgeons. Essex, CT, USA: Cunniff-Dixon Foundation; 2009.
3. Wagman LD. Progress in palliative surgery-is it a subspecialty? J Surg Oncol. 2007;96(6):449–50.
4. Ng A, Easson AM. Selection and preparation of patients for surgical palliation. Surgical Palliative Care. New York: Oxford University Press; 2004. p. 16–32.
5. Hanna NN, Bellavance E, Keay T. Palliative surgical oncology. Surg Clin North Am. 2011;91(2):343–53. viii.
6. Collins LK, Goodwin JA, Spencer HJ, Guevara C, Ferrell B, McSweeney J, et al. Patient reasoning in palliative surgical oncology. J Surg Oncol. 2013;107(4):372–5.

7. Kostakou E, Rovina N, Kyriakopoulou M, Koulouris NG, Koutsoukou A. Critically ill cancer patient in intensive care unit: issues that arise. J Crit Care. 2014;29(5):817–22.
8. Paul Olson TJ, Pinkerton C, Brasel KJ, Schwarze ML. Palliative surgery for malignant bowel obstruction from carcinomatosis: a systematic review. JAMA Surg. 2014;149(4):383–92.
9. Greer JA, Jackson VA, Meier DE, Temel JS. Early integration of palliative care services with standard oncology care for patients with advanced cancer. CA Cancer J Clin. 2013;63(5):349–63.
10. Maltoni M, Caraceni A, Brunelli C, Broeckaert B, Christakis N, Eychmueller S, et al. Prognostic factors in advanced cancer patients: evidence-based clinical recommendations--a study by the Steering Committee of the European Association for Palliative Care. J Clin Oncol. 2005;23(25):6240–8.
11. Gwilliam B, Keeley V, Todd C, Gittins M, Roberts C, Kelly L, et al. Development of prognosis in palliative care study (PiPS) predictor models to improve prognostication in advanced cancer: prospective cohort study. BMJ. 2011;343:d4920.
12. Bukki J. Recommendations for bowel obstruction with peritoneal Carcinomatosis by Laval et al. J Pain Symptom Manage. 2014.
13. Frago R, Ramirez E, Millan M, Kreisler E, del Valle E, Biondo S. Current management of acute malignant large bowel obstruction: a systematic review. Am J Surg. 2014;207(1):127–38.
14. Laval G, Marcelin-Benazech B, Guirimand F, Chauvenet L, Copel L, Durand A, et al. Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manage. 2014;48(1):75–91.
15. Shariat-Madar B, Jayakrishnan TT, Gamblin TC, Turaga KK. Surgical management of bowel obstruction in patients with peritoneal carcinomatosis. J Surg Oncol. 2014;110(6):666–9.
16. Ly J, O'Grady G, Mittal A, Plank L, Windsor JA. A systematic review of methods to palliate malignant gastric outlet obstruction. Surg Endosc. 2010;24(2):290–7.
17. Jeurnink SM, Steyerberg EW, Vleggaar FP, van Eijck CH, van Hooft JE, Schwartz MP, et al. Predictors of survival in patients with malignant gastric outlet obstruction: a patient-oriented decision approach for palliative treatment. Dig Liver Dis. 2011;43(7):548–52.
18. Fiori E, Lamazza A, Demasi E, Decesare A, Schillaci A, Sterpetti AV. Endoscopic stenting for gastric outlet obstruction in patients with unresectable antro pyloric cancer. Systematic review of the literature and final results of a prospective study. The point of view of a surgical group. Am J Surg. 2013;206(2):210–7.
19. Jeurnink SM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc. 2010;71(3):490–9.
20. Gurusamy KS, Kumar S, Davidson BR. Prophylactic gastrojejunostomy for unresectable periampullary carcinoma. Cochrane Database Syst Rev. 2013;2, CD008533.
21. Tan CJ, Dasari BV, Gardiner K. Systematic review and meta-analysis of randomized clinical trials of self-expanding metallic stents as a bridge to surgery versus emergency surgery for malignant left-sided large bowel obstruction. Br J Surg. 2012;99(4):469–76.
22. van Hooft JE, van Halsema EE, Vanbiervliet G, Beets-Tan RG, DeWitt JM, Donnellan F, et al. Self-expandable metal stents for obstructing colonic and extracolonic cancer: European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. Endoscopy. 2014;46(11):990–1053.
23. Masi G, Cupini S, Marcucci L, Cerri E, Loupakis F, Allegrini G, et al. Treatment with 5-fluorouracil/folinic acid, oxaliplatin, and irinotecan enables surgical resection of metastases in patients with initially unresectable metastatic colorectal cancer. Ann Surg Oncol. 2006;13(1):58–65.
24. Loupakis F, Cremolini C, Masi G, Lonardi S, Zagonel V, Salvatore L, et al. Initial therapy with FOLFOXIRI and bevacizumab for metastatic colorectal cancer. N Engl J Med. 2014; 371(17):1609–18.
25. Zhao XD, Cai BB, Cao RS, Shi RH. Palliative treatment for incurable malignant colorectal obstructions: a meta-analysis. World J Gastroenterol. 2013;19(33):5565–74.
26. Cirocchi R, Farinella E, Trastulli S, Desiderio J, Listorti C, Boselli C, et al. Safety and efficacy of endoscopic colonic stenting as a bridge to surgery in the management of intestinal obstruc-

tion due to left colon and rectal cancer: a systematic review and meta-analysis. Surg Oncol. 2013;22(1):14–21.
27. Bosscher MR, van Leeuwen BL, Hoekstra HJ. Surgical emergencies in oncology. Cancer Treat Rev. 2014;40(8):1028–36.
28. Rerknimitr R, Angsuwatcharakon P, Ratanachu-ek T, Khor CJ, Ponnudurai R, Moon JH, et al. Asia-Pacific consensus recommendations for endoscopic and interventional management of hilar cholangiocarcinoma. J Gastroenterol Hepatol. 2013;28(4):593–607.
29. Webb K, Saunders M. Endoscopic management of malignant bile duct strictures. Gastrointest Endosc Clin N Am. 2013;23(2):313–31.
30. Razumilava N, Gores GJ. Cholangiocarcinoma. Lancet. 2014;383(9935):2168–79.
31. Cavazzoni E, Bugiantella W, Graziosi L, Franceschini MS, Donini A. Malignant ascites: pathophysiology and treatment. Int J Clin Oncol. 2013;18(1):1–9.
32. Sangisetty SL, Miner TJ. Malignant ascites: A review of prognostic factors, pathophysiology and therapeutic measures. World J Gastrointest Surg. 2012;4(4):87–95.
33. Becker G, Galandi D, Blum HE. Malignant ascites: systematic review and guideline for treatment. Eur J Cancer. 2006;42(5):589–97.
34. Lungren MP, Kim CY, Stewart JK, Smith TP, Miller MJ. Tunneled peritoneal drainage catheter placement for refractory ascites: single-center experience in 188 patients. J Vasc Interv Radiol. 2013;24(9):1303–8.
35. Randle RW, Swett KR, Swords DS, Shen P, Stewart JH, Levine EA, et al. Efficacy of cytoreductive surgery with hyperthermic intraperitoneal chemotherapy in the management of malignant ascites. Ann Surg Oncol. 2014;21(5):1474–9.
36. Facchiano E, Risio D, Kianmanesh R, Msika S. Laparoscopic hyperthermic intraperitoneal chemotherapy: indications, aims, and results: a systematic review of the literature. Ann Surg Oncol. 2012;19(9):2946–50.
37. Valle M, Van der Speeten K, Garofalo A. Laparoscopic hyperthermic intraperitoneal peroperative chemotherapy (HIPEC) in the management of refractory malignant ascites: A multiinstitutional retrospective analysis in 52 patients. J Surg Oncol. 2009;100(4):331–4.
38. White MA, Agle SC, Padia RK, Zervos EE. Denver peritoneovenous shunts for the management of malignant ascites: a review of the literature in the post LeVeen Era. Am Surg. 2011;77(8):1070–5.
39. Paice JA, Von Roenn JH. Under- or overtreatment of pain in the patient with cancer: how to achieve proper balance. J Clin Oncol. 2014;32(16):1721–6.
40. Portenoy RK, Ahmed E. Principles of opioid use in cancer pain. J Clin Oncol. 2014;32(16):1662–70.
41. Hui D, Bruera E. A personalized approach to assessing and managing pain in patients with cancer. J Clin Oncol. 2014;32(16):1640–6.
42. Gough N, Miah AB, Linch M. Nonsurgical oncological management of cancer pain. Curr Opin Support Palliat Care. 2014;8(2):102–11.
43. Auret K, Schug SA. Pain management for the cancer patient—current practice and future developments. Best Pract Res Clin Anaesthesiol. 2013;27(4):545–61.
44. Ripamonti CI, Santini D, Maranzano E, Berti M, Roila F, ESMO Guidelines Working Group. Management of cancer pain: ESMO Clinical Practice Guidelines. Ann Oncol. 2012;23 Suppl 7:vii139–54.
45. Gordon P, LeGrand SB, Walsh D. Nausea and vomiting in advanced cancer. Eur J Pharmacol. 2014;722:187–91.
46. Old JL, Swagerty D. A practical guide to palliative care. Philadelphia: Wolters Kluwer Health; 2007. p. xii, 348.
47. Clemens KE, Faust M, Jaspers B, Mikus G. Pharmacological treatment of constipation in palliative care. Curr Opin Support Palliat Care. 2013;7(2):183–91.

Chapter 19
Adenocarcinoma of the Pancreas

Amélie Tremblay St-Germain, Steven Gallinger, Paul J. Karanicolas, and Carol-anne E. Moulton

Introduction

Pancreatic cancer is the tenth most common cancer with an incidence of 9 per 100,000 and approximately 4700 new diagnosis per year in Canada. It has one of the lowest relative survival rates, making it the fifth most common cause of cancer death [1].

By 2030, pancreas cancer is projected to remain the tenth most common cancer diagnosis but will surpass breast, prostate, and colorectal cancers to become the second cause of cancer-related death after lung cancer [3].

There is great variability among ethnic groups with Northern, Central, and Eastern Europeans and African Americans having high incidence rates of 10–15/100,000 whereas Asians and native Africans have low rates of <1/100,000 [2].

Presentation	Prognosis 5-year overall survival (OS)
• Resectable disease (10–20 %)	15–34 %
• Borderline resectable disease (5–10 %)	15–20 %
• Unresectable disease—locally advanced (20–40 %)	<5 %
• Metastatic disease (40–60 %)	0 %

The most significant risk factor for the development of pancreatic cancer is age, with a rapid rise in incidence after the age of 50. A few rare, genetic disorders contribute to up to 10–15 % of cases [4–7].

A.T. St-Germain, M.D., F.R.C.S.C. (✉)
Hepatopancreatobiliary Surgery, University of Toronto, Toronto, ON, Canada
e-mail: amelietremblaystg@gmail.com

S. Gallinger, M.D., M.Sc., F.R.C.S.C. • P. Karanicolas, M.D., Ph.D., F.R.C.S.C.
C.-a.E. Moulton, M.D., Ph.D., F.R.A.C.S.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: steven.gallinger@uhn.ca; Paul.Karanicolas@sunnybrook.ca;
Carol-anne.Moulton@uhn.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_19

Genetic disorder	Gene implicated	Approximate relative risk
• Hereditary pancreatitis	• SPINK1/PRSS1	• 50–70
• Peutz–Jeghers syndrome	• LKB1/STK11	• >100
• Cystic fibrosis	• CFTR	• 2,6–60
• Familial atypical, multiple-mole melanoma	• CDKN2A	• 13–39
• Hereditary breast ovarian cancer syndrome	• BRCA1/2	• 2,3–10
• Hereditary non-polyposis colon cancer, Lynch syndrome	• MSH2, MLH1, MSH6, PMS2	• 4–5
• Familial adenomatous polyposis	• APC	• 4–5
• Li–Fraumeni	• p53	• Unknown
• Familial pancreatic cancer	• Multiple, unidentified	• 4–32

- The recognition of the presence of an underlying genetic disorder may have significant implications for the treatment of pancreatic cancer. For example, some patients with a BRCA mutation who develop pancreatic cancer have exceptional response to platinum based chemotherapy, some demonstrating significant tumor regression, even with metastatic disease [8].
- Smoking has been clearly causally related to an increased risk of pancreatic cancer in epidemiological studies and the risk increases with extent of exposure. Diabetes, obesity, and chronic pancreatitis are more controversial. While statistical associations exist, the relative risk is low (1.2–1.5) and it is difficult to confirm causality [9].
- There is no evidence to support screening of pancreas cancer in the general population but there are surveillance guidelines for high risk individuals with Peutz–Jeghers syndrome, known BRCA mutation, familial pancreatic cancer and hereditary pancreatitis. The diagnostic yield screening in these groups varies from 1 to 50 % [7, 10, 11]. Subjects from high risk families should be enrolled in investigational protocols.

Diagnosis and Staging

Work-Up

- History and physical exam
- Performance status assessment
- Labs:
  - Liver function tests
  - Coagulation profile
  - Serum CA 19.9
- Imaging:
  - CT scan of the abdomen (pancreas protocol)
  - Chest imaging (ideally CT chest but X-ray also accepted)

Consider EUS, MRI, and/or staging laparoscopy in selected cases (see below).

A careful examination of performance status is essential, as it may greatly affect the sequencing and choice of treatment. Performance status is one of the primary indicators of long-term survival in patients with metastatic disease.

Tumor marker CA 19.9 should be performed. High levels, >150–300 μmol/L are an indicator of advanced disease and poor prognosis. Results should be interpreted with caution, however, as strict cutoff levels have not been established and jaundice artificially elevates serum levels [12].

Classification and Staging

The tumor is located in the head of the pancreas or the uncinate process in approximately 45 % of the cases. If these tumors are deemed resectable, patients should be offered a pancreatoduodenectomy (PD—Whipple procedure). When the tumor is located in the body-tail and judged resectable, distal pancreatectomy with splenectomy is the procedure of choice. Among the resectable cases, 80 % of the tumors are located in the head/uncinate.

The most well-established, CT-based classification was developed at the M. D. Anderson Cancer Center (MDACC) and uses key parameters based on preoperative, multidetector CT imaging. This classification is accepted by AHPBA, SSO, and SAT since 2009 and was incorporated into the NCCN guidelines since then.

The American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) TNM 7th edition staging system is the recommended staging system for pathology report. It provides useful prognostic information to guide treatment based on pathological findings.

	Metastatic disease	Nodal disease	Relationship to SMV-PV	Relationship to arteries
Resectable disease (RES) (all criteria must be met)	• None	• Allowed within regional nodes	• No evidence of PV or SMV distortion	• Normal tissue planes
Borderline Resectable (BOR) (any criteria fulfilled)	• None	• Allowed within regional nodes	• Venous involvement of PV or SMV with distortion, narrowing or occlusion of the vein • Must be suitable for reconstruction • Contact with IVC	• Tumor contact with CHA or variant of arterial anatomy • Tumor contact with SMA 0–180° • Body-tail tumor with tumor contact with CA 0–180°

(continued)

(continued)

	Metastatic disease	Nodal disease	Relationship to SMV-PV	Relationship to arteries
Unresectable—Locally Advanced (LA) (any criteria fulfilled)	• None	• Allowed within regional nodes	• Unreconstructible PV and/or SMV occlusion	• SMA > 180° • CA > 180° • Aortic invasion
Metastatic disease	• Yes (e.g., peritoneum, liver, lung, bones)	• Non-regional lymph node metastasis (e.g., celiac, peri-aortic)	• Any	• Any

Based on NCCN Criteria defining resectability status (Version 1.2015) [13, 14]
CA celiac axis, *CHA* common hepatic artery, *PV* portal vein, *SMA*: superior mesenteric artery, *SMV* superior mesenteric vein

Imaging Studies

- CT scan of the abdomen:
  - Biphasic arterial and pancreatic phase multi-detector CT scan with a high quality scanner is mandatory for accurate preoperative staging of pancreatic cancer and represents the single best test for determining resectability [15, 16].
  - If possible, CT should be performed prior to any interventional endoscopic procedure, as both biliary decompression and lesion biopsy can result in pancreatitis that can preclude the necessary detailed anatomical evaluation of the lesion.
  - The addition of the borderline resectable category identifies a group of patients at higher risk for positive margins and worse outcomes who may benefit from neoadjuvant therapy [17].
  - CT should be evaluated with detailed comments on the following [18]:
    - Presence or suspicion of metastatic disease (e.g., liver, peritoneum, omentum)
    - Presence or suspicion of nodal disease outside the resected field (peri-aortic and celiac nodes)
    - Presence of a hypodense mass and/or pancreatic duct dilatation and/or biliary duct dilatation
    - Presence of SMV-PV involvement and/or arterial involvement including name of the vessel with degree of involvement and/or presence of aberrant vascular anatomy
- Magnetic Resonance Imaging (MRI)
  - Magnetic resonance cholangio-pancreatography (MRCP) may have a role in diagnosis for patients with a differential diagnosis of distal common bile duct tumors (CBD), cystic pancreatic lesions.
  - MRI can be useful when CT is contraindicated.

  - MRI is less sensitive for detecting pancreatic lesions than CT and is equivalent for determining resectability.
  - Equivocal hepatic lesions may be better defined with MRI [19] or transabdominal US.

- Endoscopic Ultrasound (EUS):
  - Diagnostic EUS may be useful when:
    - A lesion is not clearly visible, despite associated pancreatic duct/common bile duct dilatation
    - To allow fine needle aspiration of the primary lesion for tissue diagnosis if needed
  - It is also useful when highly suspicious nodes in the peri-aortic and celiac area are identified on CT that, if confirmed metastatic, would preclude surgical resection.
  - Due to the increasing use and investigation of neoadjuvant treatments, there is a growing role for EUS to obtain preoperative tissue diagnosis.

- PET/CT Scan:
  - The role of PET/CT in the diagnosis and staging of pancreatic cancer is controversial.
  - PET/CT does not appear to have sensitivity advantage over CT alone in identifying small volume metastatic hepatic or peritoneal disease.

Tissue Diagnosis

A biopsy should not be performed in patients with a classical clinical presentation and imaging findings who will undergo surgery up front.

Tissue diagnosis will be necessary for patients with unresectable and metastatic disease. It can be obtained following an ERCP procedure when brushings are positive. Otherwise, the pancreatic lesion or suspected liver metastasis could be targeted.

When the pancreas lesion is targeted, endoscopic ultrasound-fine needle aspiration (EUS-FNA) has the best overall operating characteristics and is most cost-effective; however CT or US-guided percutaneous biopsy is also acceptable [20].

A lesion biopsy is advisable in patients undergoing neoadjuvant therapy and EUS-FNA should be favored when ERCP is not indicated and/or brushings are negative.

Staging Laparoscopy

Staging laparoscopy should be reserved for selected cases where the yield is likely to justify the additional procedural risks and costs [21]. The literature suggests that 10–36 % of patients can be spared an unnecessary laparotomy [22]. As a guide, patients with tumors >3 cm, tumors in the neck, body or tail, or with equivocal CT findings for metastatic disease, may benefit from laparoscopy [23].

Management

Classification	Neoadjuvant therapy	Surgery	Adjuvant treatment	Follow-up (F/U)
• Resectable disease (RES)	• Under investigation	• Resection	• Chemotherapy × 6 months should be initiated within 12 weeks • Gemcitabine × 6 months	• Initial follow-up 2–4 weeks • H&P q 3–6 months × 2 years, then annually • Include assessment for pancreatic insufficiency • Consider CT and CA 19-9 q 3–6 months × 2 year (level 5) • There is no data to support that aggressive postoperative surveillance alters outcome in this disease.
• Borderline resectable (BOR)	• **Very controversial**: **resection vs. neoadjuvant therapy**. • Patients should be included in clinical trials if possible • Consider neoadjuvant therapy • Decision to proceed to surgery is usually based on "non-progression"	• **Borderline-Vein**: Consider up-front surgery. Will likely require a PV-SMV resection and reconstruction. • **Borderline-Artery**: Consider neoadjuvant therapy. If up-front surgery, early exploration to define arterial involvement is necessary to guide intra-op decision. Resectability status should be based on ability to obtain negative margin	• Chemotherapy × 6 months (same as resectable) • Patients who have received neoadjuvant therapy may be candidates for additional chemotherapy	• Same as RES
• Unresectable—locally advanced (LA)	• Chemotherapy with palliative intent (same as metastatic) • Biliary decompression with stent where indicated • When found during surgical exploration; consider surgical biliary ± gastric bypass • Trials underway to evaluate neoadjuvant treatment followed by resection for very selected patients with arterial involvement [26]			

(continued)

(continued)

Classification	Neoadjuvant therapy	Surgery	Adjuvant treatment	Follow-up (F/U)
• Metastatic disease	• Chemotherapy with palliative intent FOLFIRINOX (preferred) or Gemcitabine–paclitaxel (preferred) or Gemcitabine (for patients with poor performance status) • Biliary decompression with stent where indicated • When found during surgical exploration; consider surgical biliary ± gastric bypass			

Special Notes

- In the setting of good imaging techniques, exploratory laparotomy for the purpose of determining resectability should be avoided.
- Surgical biliary ± gastric bypass are recommended at the time of exploration if the disease is deemed unresectable or metastatic and patient has an expected survival greater than 12 months (good performance status, absence of risk factors of poor survival) [27].
- The Arterial Resection for Cancer of the Pancreas trial (ARCAP) protocol at the University of Toronto is examining the role of neoadjuvant therapy followed by concurrent chemoradiotherapy, followed by arterial resection and reconstruction in patients with Borderline Resectable and Locally Advanced disease with arterial involvement [26].

Neoadjuvant Therapy: Rationale

Surgery alone, even for resectable pancreatic cancer, often leads to poor outcomes. Due to the relatively high morbidity of the procedure, only 59–95 % of the patients have adequately recovered to receive adjuvant chemotherapy within 3 months of resection [28, 29]. In addition, the aggressive nature of pancreas cancer and its high propensity to metastasize are arguments in favor of earlier systemic treatments.

There is a major concern regarding the "loss of the surgical window" with local progression that could preclude surgery. In two meta-analysis [30, 31], 16–21 % of patients progressed during neoadjuvant therapy. Most patients who progressed developed metastases during the induction therapy and were not offered surgery. This subgroup of patients with very poor cancer biology may be spared a futile operation. In this regard, neoadjuvant therapy may increase the ability to identify patients who are more likely to benefit from surgery.

The goal of neoadjuvant therapy is to improve DFS and OS in the setting of resectable disease and to improve resection rate and margin-clear resections (R0) in the setting of borderline resectable or unresectable disease. The role of neoadjuvant therapy for pancreas cancer has not been clearly defined and there is a tremendous variability of its use worldwide. Patients with resectable or borderline disease

should be offered the opportunity to participate in clinical trials examining this question where available.

To date, there is only one randomized controlled study comparing neoadjuvant therapy vs. up-front surgery in the setting of resectable or borderline disease but many studies are currently recruiting [32–36]. In this multicenter study [37], 66 patients with resectable disease were randomized to surgery vs. neoadjuvant chemoradiotherapy (gemcitabine and cisplatin plus radiotherapy 50,4 Gy) plus surgery and both groups received adjuvant gemcitabine. Unfortunately, the trial was terminated early due to slow accrual. Median OS was 14.4 vs. 17.4 months with an intention-to-treat analysis and 18.9 vs. 25.0 months after resection.

The currently available data comes from small and heterogenous retrospective studies and phase 1–2 studies. In general, neoadjuvant regimens with CT restaging have shown partial response (PR) in 0–31 %, stable disease (SD) in 60 % and progression (PD) in 17–32 %. Interestingly, in the previously resectable group, 0–17 % of the specimens have shown complete histological responses. In selected patients with Locally Advanced Pancreas Cancer (LAPC), neoadjuvant therapy can allow resection in up to 20–40 % of LAPC patients. Once resection has been achieved, overall survival appears to be comparable to that observed for primarily resectable patients [38, 39].

FOLFIRINOX based regimens have been studied in selected patients with borderline resectable or LAPC and have shown PR in 28–44 % with resection made possible in 22–67 % and an overall R0 rate of 28–67 % [38, 40–42].

FOLFIRINOX, gemcitabine–paclitaxel, and chemoradiation protocols have been introduced into novel multimodality treatment, but further study is required to clarify the optimal strategy.

Surgery

- Outcomes following pancreatoduodenectomy (PD) vary widely with the volume of cases performed. This is reflected in both early mortality (from 16 % in low volume to <4 % in high volume centers) and 3-year survival (25 % vs. 37 %, respectively).
- Recent series from high volume centers reported peri-op mortality between 1 and 2 %, median LOS of 6–9 days, and median OS of 22–27 months after PD for pancreas cancer [28, 29].
- 20–25 % of the surgeries included a PV-SMV resection and reconstruction.
- Positive surgical margins occur in 13–50 % of patients undergoing resection.
- Clinical Pathways to standardize and enhance recovery after PD have been shown to shorter the LOS without increasing morbidity, mortality or readmission rate.
- Laparoscopic PD for pancreas cancer is feasible and safe in experienced hands. It may decrease LOS and time to adjuvant chemotherapy and prolong PFS [29].

Adjuvant Therapy

- Adjuvant therapy is recommended for most patients following surgical resection and improves long-term survival (5 years OS increases from 11 to 22 % with gemcitabine vs. observation) [43].
- The current standard of care in Ontario is postoperative chemotherapy with gemcitabine for 6 months post resection and should be started within 3 months of surgery.
- While there has been no evidence demonstrating superiority of gemcitabine over 5-FU based chemotherapy, gemcitabine has a lower toxicity profile [44].
- Recent publications suggest that FOLFIRINOX has superior oncologic outcomes but increased toxicity compared with gemcitabine in the palliative setting [45]. Clinical trials are underway examining its use in the adjuvant and neoadjuvant setting for patients with good performance status [32, 46].

Biliary Decompression

Preoperative decompression should be used selectively, as routine biliary drainage increases the rate of perioperative infectious complications, in addition to the risks of the procedure itself [24].

Presentation	Recommendation	Procedure
Cholangitis	• Urgent Biliary Decompression	• ERCP + 10Fr plastic stent or SEMS
Preoperative elective	• Routine biliary drainage is not recommended in mild/moderate jaundice due to higher overall risks • Selective approach is recommended with consideration for stent if severe jaundice AND expected delay to surgery (>7–10 days)	• ±ERCP + 10Fr plastic stent or short metal stent
Consideration for neo-adjuvant therapy	• Self-expanding metal stents should be considered.	• ERCP + short metal stent
Unresectable or metastatic	• Consider stent if symptomatic or elevated bilirubin • The choice of metallic or plastic stent depends on life expectancy. • The significantly higher price of SEMS suggests their use in selected cases (life expectancy > 3 months) [25]	• ERCP + SEMS or 10Fr plastic stent

ERCP endoscopic retrograde cholangio-pancreatography; *SEMS* self-expanding metal stent

Technical Aspects of Surgery

Multiple controversies exist regarding various technical aspects of pancreatic resection and reconstruction. These are summarized here:

	Evidence	Recommendation
Extended lymphadenectomy vs. regular [47, 48]	• No survival advantage with extended lymphadenectomy, increased early morbidity	• Standard lymphadenectomy
Venous resection [49–51]	• Need for venous resection does not impact survival if R0 resection obtained	• Venous resection is standard of care if reconstruction is possible and R0 resection is obtainable
PPPD vs. standard [52, 53]	• No difference in clinically relevant outcome between the two techniques	• PPPD and Standard Whipple are acceptable
PJ vs. PG [54]	• Meta-analysis shows no difference in overall morbidity, DGE, bleeding, reoperation, or mortality. • Decreased incidence of POPF and intra-abdominal collection with PG	• PJ and PG are acceptable • Consider PG in high-risk pancreas[a]
Pancreatic duct stent [55]	• No evidence of difference in leak rate	• Consider stent in high-risk pancreas[a]
Somatostatin analogues [56–58]	• Conflicting data from European and US trials • Meta-analysis suggests reduction in POPF rate [56, 57] • Recent RCT suggests a decreased rate of clinically significant POPF from 21 to 9 % [58] • No difference in mortality	• Consider administration of peri-op somatostatin analogues
Intra-abdominal drain [59–61]	• Conflicting data • Multicenter RCT suggests advantage to use routine placement of drain post-PD : significant reduction of complication ≥ grade 2 [60]	• Selective use of drain • Early drain removal (on POD 3) [61]

(continued)

(continued)

	Evidence	Recommendation
Open vs. laparoscopic distal pancreatectomy (DP)	• Systematic review and meta-analysis: lap DP could decrease EBL, transfusion rate, LOS, and infections [62] • Small retrospective series of 23 Lap DP for pancreas cancer: similar short- and long-term oncologic outcomes as compared with open technique, with potentially shorter hospital stay [63]	• Laparoscopic DP for pancreas cancer is feasible and safe in experienced hands.
Open vs. laparoscopic pancreatoduodenectomy (PD) [29]	• Large retrospective series of 108 totally laparoscopic PD for pancreatic ductal adenocarcinoma (PDAC) • Decreased EBL, transfusion rate, LOS, DGE grade B/C, and time to adjuvant chemotherapy. • No difference in R0 rate, OS. • Improved PFS.	• Laparoscopic PD for pancreas cancer is feasible and safe in experienced hands.

DGE delayed gastric emptying, *PJ* pancreatojejunostomy, *PG* pancreatogastrostomy, *POPF* postoperative pancreatic fistula, *PPPD* pylorus preserving pancreatoduodenectomy, *EBL* estimated blood loss, *LOS* lenght of stay, *DGE* delayed gastric emptying
[a]Soft gland or small pancreatic duct

Special Situation

- Patients with large lesions of the neck or body, or associated main duct intraductal papillary mucinous neoplasm (IPMN) may require total pancreatectomy and splenectomy.

Landmark Trials Adjuvant and Neoadjuvant Therapy

	Publication	Year	Main findings
Adjuvant chemoradiotherapy	EORTC-GITG [64]	1985	• NS improvement in OS—discouraged use of adjuvant chemoradiotherapy
Adjuvant chemoradiotherapy vs. chemotherapy alone	ESPAC-1 [65]	2001 (Lancet)	• 5 years OS chemotherapy (20 %) vs. chemoradiotherapy (10 %)
Adjuvant gemcitabine vs. observation	CONKO-001 [43]	2007 (JAMA)	• DFS 13.4 vs. 6.9 months • 5 years OS 22.5 % vs. 11.5 %

(continued)

(continued)

	Publication	Year	Main findings
Adjuvant 5-FU vs. gemcitabine	ESPAC-3 [44]	2010 (JAMA)	• No difference in median survival (23 months), fewer adverse events with gemcitabine
FOLFIRINOX vs. gemcitabine (metastatic)	PRODIGE 4 (Accord 11) Trial [45]	2011 (NEJM)	• Median survival 11.1 months vs. 6.8 months • Increased toxicity with FOLFIRINOX, reserved for ECOG performance status 0 and 1 patients
Gemcitabine–paclitaxel vs. gemcitabine (metastatic) [66]		2013 (NEJM)	• Median survival 8.5 months vs. 6.7 months • Slightly increased toxicity with gemcitabine–paclitaxel

NS nonsignificant, *OS* overall survival, *DFS* disease-free survival, *ECOG* Eastern Cooperative Oncology Group

Referring to Medical Oncology

1. All patients who underwent resection **should** be referred for adjuvant chemotherapy.
2. Patients with unresectable or metastatic disease **should** be referred for consideration of definitive treatment.
3. Patients with borderline disease **could** be referred preoperatively for consideration of neoadjuvant treatment in the setting of a clinical trial.
4. Patients with unresectable/locally advanced disease **could** be considered for neoadjuvant therapy in the setting of a clinical trial.

Referring to Radiation Oncology

1. Patients with unresectable disease **could** be referred for consideration of radiotherapy as an adjunct to chemotherapy.
2. The routine use of radiotherapy in the adjuvant setting remains controversial. Patients who underwent resection and had positive margins **could** be referred for consideration of adjuvant radiotherapy.

Referring to Multidisciplinary Cancer Conference (MCC)

1. All patients should be presented early for multidisciplinary review to enable appropriate and efficient sequencing of investigations and treatments.
2. All patients should be offered to participate in clinical trials when available and appropriate for their stage and situation.

Toronto Pearls

- High quality CT imaging with biphasic pancreas protocol is essential for accurate staging and operative planning.
- All patients should be presented early for multidisciplinary review at a high volume HPB center to enable appropriate and efficient sequencing of investigations and treatments.
- The sequencing of treatment should be individualized.
- Patients should routinely be given an opportunity to participate in clinical trials.
- Reconstructible venous involvement requires PV and/or SMV resection and reconstruction. The procedure is considered technically safe therefore this subgroup of borderline disease is treated like resectable disease.
- Arterial involvement does not absolutely preclude resection. Whether these tumors are classified as "Borderline-Artery" or "Locally Advanced-Unresectable," the cases should be reviewed at a tertiary center. These patients should be given an opportunity to participate in trials or clinical protocols and considered for neoadjuvant chemotherapy [26].

References

1. Canadian Cancer Society, Canadian Cancer Statistics 2014
2. Canadian Cancer Society's Steering Committee on Cancer Statistics. Canadian Cancer Statistics 2011. Toronto: Canadian Cancer Society; 2011.
3. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res. 2014;74(11):2913–21.
4. Lowenfels AB, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. Med Clin North Am. 2000;84(3): 565–73.
5. Jiao L, Li D. Epidemiology and prospects for prevention of pancreatic cancer. In: Neoptolemos JP et al., editors. Pancreatic cancer. New York, NY: Springer; 2010. p. 3–25.
6. Stoita A. Review of screening for pancreatic cancer in high risk individuals. World J Gastroenterol. 2001;17:2365–71.
7. Del Chiaro M, Segersvärd R, Lohr M, et al. Early detection and prevention of pancreatic cancer: is it really possible today? World J Gastroenterol. 2014;20(34):12118–31.
8. Sonnenblick A, Kadouri L, Appelbaum L, et al. Complete remission, in BRCA2 mutation carrier with metastatic pancreatic adenocarcinoma, treated with cisplatin based therapy. Cancer Biol Ther. 2001;12:165–8.
9. Iodice S, Gandini S, Maisonneuve P, et al. Tobacco and the risk of pancreatic cancer: a review and meta-analysis. Langenbeck's Arch Surg. 2008;393:535–45.
10. Brand RE, Lerch MM, Rubinstein WS, et al. Recent advances in counseling and surveillance of patients at risk for developing pancreatic cancer. Gut. 2007
11. Greer J, Brand RE. Screening for pancreatic cancer: current evidence and future directions. Gastroenterol Hepatol. 2007;3(12)
12. Boeck S, Stieber P, Holdenrieder S, et al. Prognostic and therapeutic significance of carbohydrate antigen 19-9 as tumor marker in patients with pancreatic cancer. Oncology. 2006;70(4):255–64.
13. NCCN Guidelines Version 1.2015 Pancreatic Adenocarcinoma

14. Callery MP, Chang KJ, Fishman EK, et al. Pretreatment assessment of resectable and borderline resectable pancreatic cancer: expert consensus statement. Ann Surg Oncol. 2009;16(7):1727–33.
15. Tamm E, Charnsangavej C, Szklaruk J. Advanced 3-D imaging for the evaluation of pancreatic cancer with multidetector CT. Int J Gastrointest Cancer. 2001;30(1):65–71.
16. Prokesch RW, Schima W, Chow LC, Jeffrey RB. Multidetector CT of pancreatic adenocarcinoma: diagnostic advances and therapeutic relevance. Eur Radiol. 2003;13(9):2147–54.
17. Varadhachary GR, Tamm EP, Abbruzzese JL, et al. Borderline resectable pancreatic cancer: definitions, management, and role of preoperative therapy. Ann Surg Oncol. 2006;13(8):1035–46.
18. Al-Hawary MM, Francis IR, Chari ST, et al. Pancreatic ductal adenocarcinoma radiology reporting template: consensus statement of the society of abdominal radiology and the American pancreatic association. Gastroenterology. 2014;146(1):291–304.
19. Turowska A, Łebkowska U, Kubas B, et al. The role of magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) in the diagnosis and assessment of resectability of pancreatic tumors. Med Sci Monit. 2007;13 Suppl 1:90–7.
20. Harewood GC, Wiersema MJ. Endosonography-guided fine needle aspiration biopsy in the evaluation of pancreatic masses. Am J Gastroenterol. 2002;97(6):1386–91.
21. Friess H, Kleeff J, Silva JC, et al. The role of diagnostic laparoscopy in pancreatic and periampullary malignancies. J Am Coll Surg. 1998;186(6):675–82.
22. Stefanidis D, Grove KD, Schwesinger WH, et al. The current role of staging laparoscopy for adenocarcinoma of the pancreas: a review. Ann Oncol. 2006;17(2):189–99.
23. Brooks AD, Mallis MJ, Brennan MF, Conlon KC. The value of laparoscopy in the management of ampullary, duodenal, and distal bile duct tumors. J Gastrointest Surg. 2002;6(2):139–45.
24. Van der Gaag NA, Rauws EA, van Eijck CH, et al. Preoperative biliary drainage for cancer of the head of the pancreas. N Engl J Med. 2010;362(2):129–37.
25. Boulay BR, Parepally M. Managing malignant biliary obstruction in pancreas cancer: choosing the appropriate strategy. World J Gastroenterol. 2014;20(28):9345–53.
26. McGilvray et al. Arterial resection for cancer of the pancreas (ARCAP): a phase II trial. Toronto General Hospital, May 2012.
27. Müller MW, Friess H, Köninger J, et al. Factors influencing survival after bypass procedures in patients with advanced pancreatic adenocarcinomas. Am J Surg. 2008;195(2):221–8.
28. Serrano PE, Cleary SP, Dhani N, et al. Improved long-term outcomes after resection of pancreatic adenocarcinoma: a comparison between two time periods. Ann Surg Oncol. 2015;22(4):1160–7.
29. Kendrick ML, et al. Total laparoscopic pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. Oncologic advantages over open approaches? Ann Surg. 2014;260:633–40.
30. Andriulli A, Festa V, Botteri E, et al. Neoadjuvant/preoperative gemcitabine for patients with localized pancreatic cancer: a meta-analysis of prospective studies. Ann Surg Oncol. 2012;19:1644–62.
31. Gillen S, Schuster T, Meyer Zum Buschenfelde C. Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010;7:e1000267.
32. Randomized Multicenter Phase II/III Study With Adjuvant Gemcitabine Versus Neoadjuvant-Adjuvant FOLFIRINOX for Resectable Pancreas Carcinoma. NCT02172976
33. ESPAC - 5F: European Study Group for Pancreatic Cancer - Trial 5F: four arm, prospective, multicentre, randomised feasibility trial of immediate surgery compared with neoadjuvant chemotherapies and neoadjuvant chemoradiotherapy.
34. Heinrich S, Pestalozzi B, Lesurtel M, et al. Adjuvant gemcitabine versus NEOadjuvant gemcitabine/oxaliplatin plus adjuvant gemcitabine in resectable pancreatic cancer: a randomized multicenter phase III study (NEOPAC study). BMC Cancer. 2011;11:346. NCT01314027.
35. Sequential neoadjuvant chemoradiotherapy (CRT) followed by curative surgery vs. primary surgery alone for resectable, non-metastasized pancreatic adenocarcinoma: NEOPA- a randomized multicenter phase III study (NCT01900327).
36. NEONAX: neoadjuvant plus adjuvant or only adjuvant nab-paclitaxel plus gemcitabine for resectable pancreatic cancer—A *phase II* study of the AIO Pancreatic Cancer Group. NCT02047513.

37. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer. Results of the first prospective randomized phase II trial. Strahlenther Onkol. 2015;191(1):7–16.
38. Bittoni A, Santoni M, Lanese A, et al. Review article. Neoadjuvant therapy in pancreatic cancer: an emerging strategy. Gastroenterol Res Pract. 2014;2014:183852. Epub 2014 Jul 1.
39. Heinemann V, Haas M, Boeck S. Neoadjuvant treatment of borderline resectable and non-resectable pancreatic cancer. Ann Oncol. 2013;24:2484–92.
40. Hosein PJ, Macintyre J, Kawamura C, et al. A retrospective study of neoadjuvant FOLFIRINOX in unresectable or borderline-resectable locally advanced pancreatic adenocarcinoma. BMC Cancer. 2012;12:199.
41. Christians KK, Tsai S, Mahmoud A, et al. Noeadjuvant FOLFIRINOX for borderline resectable pancreas cancer: a new treatment paradigm? Oncologist. 2014;19:266–74.
42. Faris JE, Blaszkowsky LS, McDermott S, et al. FOLFIRINOX in locally advanced pancreas cancer: The Massachussetts General Hospital Cancer Center Experience. Oncologist. 2013;18:543–8.
43. Oettle H, Post S, Neuhaus P, et al. Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA. 2007;297(3):267–77.
44. Neoptolemos JP, Stocken DD, Bassi C, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized control trial. JAMA. 2010;304(10):1073–81.
45. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. NEJM. 2011;364(19):1817–25.
46. A pilot study of pre- and post-surgery chemotherapy with mFOLFIRINOX in localized, resectable pancreatic adenocarcinoma. (*Phase II*) NCT01660711. (US)
47. Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy with or without distal gastrectomy and extended retroperitoneal lymphadenectomy for periampullary adenocarcinoma, part 2: randomized controlled trial evaluating survival, morbidity, and mortality. Ann Surg. 2002;236(3):355–66.
48. Tol JA, Gouma DJ, Bassi C, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery. 2014;156(3):591–600.
49. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. J Gastrointest Surg. 2004;8(8):935–50.
50. Bockhorn M, Uzunoglu FG, Adham M, et al. Borderline resectable pancreatic cancer: a consensus statement by the International Study Group of Pancreatic Surgery (ISGPS). Surgery. 2014;155(6):977–88.
51. Kim P, Wei A, Atenafu E, et al. Planned versus unplanned portal vein resections during pancreaticoduodenectomy for adenocarcinoma. Br J Surg. 2013;100(10):1349–56.
52. Diener MK, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. In: The Cochrane Collaboration, Büchler MW, editors. Cochrane database of systematic reviews. Chichester: Wiley; 2011.
53. Diener MK, Fitzmaurice C, Schwarzer G, et al. Pylorus-preserving pancreaticoduodenectomy (pp Whipple) versus pancreaticoduodenectomy (classic Whipple) for surgical treatment of periampullary and pancreatic carcinoma. Cochrane Database Syst Rev. 2011;11(5):CD006053.
54. Hallet J, Zih FS, Deobald RG, et al. The impact of pancreaticojejunostomy versus pancreaticogastrostomy reconstruction on pancreatic fistula after pancreaticoduodenectomy: meta-analysis of randomized controlled trials. HPB (Oxford). 2015;17(2):113–22.
55. Winter JM, Cameron JL, Campbell KA, et al. Does pancreatic duct stenting decrease the rate of pancreatic fistula following pancreaticoduodenectomy? Results of a prospective randomized trial. J Gastrointest Surg. 2006;10(9):1280–90. discussion 1290.
56. Connor S, Alexakis N, Garden OJ, et al. Meta-analysis of the value of somatostatin and its analogues in reducing complications associated with pancreatic surgery. Br J Surg. 2005;92(9):1059–67.

57. Alghamdi A, Jawas AM, Hart RS. Use of octreotide for the prevention of pancreatic fistula after elective pancreatic surgery: a systematic review and meta-analysis. Can J Surg. 2007;50(6):459–66.
58. Allen P, Gönen M, Brennan MF, et al. Pasireotide for postoperative pancreatic fistula. N Engl J Med. 2014;370(21):2014–22.
59. Conlon KC, Labow D, Leung D, et al. Prospective randomized clinical trial of the value of intraperitoneal drainage after pancreatic resection. Ann Surg. 2001;234(4):487–93.
60. Van Buren G, Bloomston M, Hughes SJ. A randomized prospective multicenter trial of pancreaticoduodenectomy with and without routine intraperitoneal drainage. Ann Surg. 2014;259:605–12.
61. Bassi C, Molinari E, Malleo G, et al. Early versus late drain removal after standard pancreatic resections. Results of a prospective randomized trial. Ann Surg. 2010;252:207–14.
62. Jin T, Altaf K, Xiong JJ, et al. A systematic review and meta-analysis of studies comparing laparoscopic and open distal pancreatectomy. HPB (Oxford). 2012;14(11):711–24.
63. Kooby DA, Hawkins WG, Schmidt CM, et al. A multicenter analysis of distal pancreatectomy for adenocarcinoma: is laparoscopic resection appropriate? J Am Coll Surg. 2010;210(5):779–85. 786–7.
64. Klinkenbijl JH, Jeekel J, Sahmoud T, et al. Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group. Ann Surg. 1999;230(6):776–82. discussion 782–84.
65. Neoptolemos JP, Stocken DD, Friess H, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. N Engl J Med. 2004;350(12):1200–10.
66. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. N Engl J Med. 2013;369:1691–703.

Chapter 20
Peritoneal Surface Malignancies

Mai-Kim Gervais, Anand Govindarajan, and J. Andrea McCart

Introduction

Peoneal surface malignancy can be defined as any cancer that has either originated from the peritoneum itself (primary peritoneal malignancy) or has metastasized to the peritoneum from a different primary site (secondary peritoneal malignancy). Peritoneal surface malignancies can thus be subdivided into three main categories:

Site of origin	Common histologies
Peritoneum	• Mesothelioma • Primary peritoneal carcinoma
Gastrointestinal tract (stomach, appendix, colon, rectum, pancreas)	• Mucinous cystadenocarcinoma • Intestinal/colonic-type adenocarcinoma • Signet ring cell adenocarcinoma • Goblet cell (adenocarcinoid)
Ovary	• Epithelial carcinoma

This chapter focuses on peritoneal mesothelioma and peritoneal carcinomatosis arising from the appendix, colon, and rectum.

M.-K. Gervais, M.D., F.R.C.S.C. (✉)
Fellow, General Surgical Oncolog, University of Toronto, Toronto, ON, Canada
e-mail: maikim.gervais@gmail.com

A. Govindarajan, M.D., M.Sc., F.R.C.S.C. • J.A. McCart, M.D., M.Sc., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: agovindarajan@mtsinai.on.ca; amccart@mtsinai.on.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_20

Peritoneal Carcinomatosis Arising from the Appendix

Neoplasms of the appendix have an incidence rate of 0.12–2 cases per one million people, with female predominance, and mostly develop from epithelial tumors [1]. Peritoneal carcinomatosis from mucinous tumors (pseudomyxoma peritonei) has a better prognosis than those with non-mucinous adenocarcinoma [2].

Pseudomyxoma peritonei (PMP) is defined as the accumulation of mucin in the peritoneal cavity, secondary to mucinous epithelial tumors. Ninety percent of cases originate from appendiceal tumors, but can also arise from the ovary, colon, and infrequently from pancreas, gallbladder, and urachus [3, 4]. Although the term PMP is often used to describe mucinous disease in the peritoneum secondary to a low-grade appendiceal primary, the term is best used only as a clinical description rather than a pathologic one.

PMP usually develops after rupture of the appendix and dissemination to the peritoneal cavity. Abdominal pain at the right lower quadrant similar to pain due to appendicitis is the most common clinical presentation. Appendiceal malignancy can also be found incidentally while performing a surgery for an unrelated condition (15–20 % of cases). It can also present as an abdominal mass, or as the presence of mucin in a hernial sac [4].

Terminology for peritoneal carcinomatosis arising from appendiceal tumors is varied and inconsistently applied. Two of the most commonly used classifications are:

World Health Organization (WHO) classification:

- **LAMN**: Low grade appendiceal mucinous neoplasm. It includes tumor confined to the appendix, tumor with acellular mucin outside the appendix, or tumor with extra-appendiceal disease [4].
- **MACA**: High grade mucinous adenocarcinoma. It is defined as tumor with infiltrative type invasion of the wall, with or without desmoplasia [4].

Ronnett histologic classification:

- **DPAM**: Disseminated peritoneal adenomucinosis (appendix and colorectal origin) [5, 6]. DPAM is a well-differentiated (low grade) tumor and twice as common as peritoneal mucinous carcinomatosis (PMCA) [3, 4]. It is characterized by scant strip of epithelium with minimal to moderate atypia and no significant mitotic activity [4].
- **PMCA**: Peritoneal mucinous carcinomatosis (appendix and colorectal origin), typically high grade [5, 6]. PMCA is histologically characterized by abundant proliferation of epithelium and cytologic features of carcinoma. It has a worse prognosis than DPAM [4].

At the University of Toronto, the LAMN/MACA classification is used to classify mucinous tumors of the appendix.

- Signet ring cell adenocarcinoma of the appendix is rare and associated with a poor prognosis with rapid dissemination to the peritoneal cavity. Goblet cell carcinoid (GCC) is a distinct entity from classical appendiceal carcinoid, and is

sometimes referred to as an adenocarcinoid because of its mixed neuroendocrine and epithelial immunoprofile. Tang et al. have classified GCC into three prognostic groups: typical GCC (Group A), signet ring cell adenocarcinoma ex-GCC (Group B), and poorly differentiated adenocarcinoma ex-GCC (Group C) [7].

- The American Joint Committee on Cancer (AJCC) 7th edition is the current recommended staging system for appendiceal cancers [8]. For appendiceal origin, M1a: intraperitoneal metastasis beyond the right lower quadrant, including PMP and M1b: nonperitoneal metastasis.

Improved outcomes are seen with cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) treatments (see table below). Compared to patients undergoing CRS + HIPEC, low grade appendiceal pseudomyxoma treated with debulking alone have a 10-year overall survival of 32 %. For patients with carcinomatosis from high grade adenocarcinoma of the appendix, surgery alone offers a 5-year overall survival of 6 % [9]. One of the main prognostic factors is the histologic subtype. Furthermore, the extent of peritoneal disease has less impact on prognosis in low grade than high grade disease [3].

Histologic subtypes (primary)	Classification	Prognosis overall survival[a]
• Mucoceles of the appendix – Mucosal hyperplasia – Simple or retention cyst – Mucinous cystadenoma[b] – Mucinous cystadenocarcinoma[b]	**LAMN/DPAM**	3-year: 100 % 5-year: 75–86 % 10-year: 45–68 %
	MACA/PMCA	3-year: 90 % 5-year: 14–44 % 10-year: 3 %

[a]Prognosis is with CRS + HIPEC treatments
[b]Previously termed PMP if has seeded throughout the abdomen [1, 10]

Peritoneal Carcinomatosis Arising from the Colon and Rectum

- Peritoneal carcinomatosis will affect 30 % of patients with colorectal cancer, and 5–10 % of these patients will have synchronous disease [11]. In 25 % of these cases, the peritoneal cavity seems to be the only site of metastatic disease [12].
- The American Joint Committee on Cancer (AJCC) 7th edition is the current recommended staging system for colorectal cancers [8]. For colorectal origin, M1a: metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node) and M1b: metastasis in more than one organ/site or the peritoneum. Peritoneal carcinomatosis is classified as stage IV disease.
- In recent case series and multi-institutional studies, the 5-year overall survival of patients treated for colorectal peritoneal carcinomatosis with CRS + HIPEC ranges from 20 to 51 % [12–18]. Compared to patients undergoing CRS + HIPEC,

patients with colorectal cancer and peritoneal carcinomatosis treated nonsurgically with systemic chemotherapy have 5-year overall survival of 13 % [13].
- The main prognostic factors are completeness of cytoreduction and extent of disease.

Peritoneal Mesothelioma

- There are approximately 515 cases of mesothelioma a year in Canada, 10–15 % of which are peritoneal, which is the second most common site after the pleura [19]. Asbestos is associated with peritoneal mesothelioma in 33 % of cases [20]. There is no uniformly accepted staging system for mesothelioma. This TNM staging system has been proposed by the Peritoneal Surface Oncology Group (see Table) [21].

Histologic subtypes	Staging			Prognosis 5-year OS[a]
• Well-differentiated tubulopapillary • Epithelioid • Sarcomatoid • Biphasic (a mix of epithelioid and sarcomatoid)	T	N	M	–
	• T1 = PCI 1–10 • T2 = PCI 11–20 • T3 = PCI 21–30 • T4 = PCI 31–39	• N0 • N1	• M0 • M1	
	• Stage 1 (T1N0M0)			87 %
	• Stage 2 (T2-3N0M0)			53 %
	• Stage 3 (T4 or N1 or M1)			29 %

OS overall survival, *PCI* Peritoneal Cancer Index, *N1* any nodal disease present, *M1* any distant spread
[a]Prognosis is with CRS + HIPEC treatments

- Elias et al. classify peritoneal mesothelioma into three subtypes: "low grade" including papillary, adenomatoid, and multicystic mesothelioma, "intermediate grade" including epithelioid subtype, and "high grade" including sarcomatoid and biphasic subtypes, which have the worst prognosis [3, 22, 23]. CRS + HIPEC are generally not offered in peritoneal mesothelioma presenting with sarcomatoid and biphasic subtypes, neither for mesothelioma presenting with nodal disease. Presence of these features correlates with poor prognosis and no significant oncologic benefit from surgery. Compared to patients undergoing CRS + HIPEC, median survival for untreated mesothelioma is 6 months, and patients treated with chemotherapy alone (pemetrexed and cisplatin based regimen) can expect a median overall survival between 10 and 26.8 months [20].
- Main prognostic factors are histologic subtype, extent of disease, and completeness of cytoreduction. Mortality of peritoneal mesothelioma is often secondary to disease progression in peritoneum and not due to distant metastases.

Management

Management of peritoneal malignancies can include CRS + HIPEC, chemotherapy, surgery alone, or palliative treatment only. The best results are achieved when a patient is able to undergo a complete cytoreduction. Patient selection to determine those who will benefit from CRS and HIPEC is critical.

Cytoreductive Surgery (CRS) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

- Cytoreductive surgery is the first step of the procedure, and the extent of resection is assessed using the peritoneal carcinomatosis index (PCI) score. CRS generally includes resection of organs affected by peritoneal disease, followed by peritoneal stripping of involved surfaces of the abdomen, diaphragm, and pelvis. Electro-evaporation of small implants on serosa of small bowel, liver capsule, and other solid viscera is then undertaken, using fulguration by electrocautery or argon beam coagulation.
- An incomplete resection of peritoneal carcinomatosis from colorectal cancer is not usually recommended, as median survival with incomplete resection equates to that with systemic chemotherapy alone.
- The administration of HIPEC follows the cytoreductive phase of the operation. HIPEC consists of intraoperative perfusion of the abdominal cavity with heated chemotherapy solution for a specific length of time. The two main intraperitoneal agents used are oxaliplatin and mitomycin-C (MMC). Those agents are heated between 40 and 43 °C, for 30–90 min. Intravenous infusion of 5-FU and leucovorin are given preceding intraperitoneal oxaliplatin treatment in colorectal carcinomatosis. There is however no international consensus on the standard agent or dosing for HIPEC treatment [24].
- Intraperitoneal chemotherapy cannot penetrate more than 2–3 mm depth and thus, it is generally administered only after a CC-0 or CC-1 resection. HIPEC can be performed in a closed or open technique, with no documented differences in outcomes between the two methods. It has been shown that heating the chemotherapy allows for better penetration into tissues and potentiates the cytotoxicity of the chemotherapeutic agent [25–27]. The hyperthermia itself is also thought to have an independent cytotoxic effect [28]. The addition of HIPEC to CRS has been shown to be associated with improved outcomes in non-randomized studies only. Prodige 7 is a phase III French multicenter randomized controlled trial comparing complete CRS + HIPEC vs. CRS alone for peritoneal metastases arising from colorectal cancer with PCI <25. Its aim is to determine and quantify the impact of HIPEC in terms of survival. Accrual is now completed and results are awaited (NCT00769405).

- No standard intraperitoneal chemotherapy protocol has been universally adopted. A comparative study between intraperitoneal administration of MMC vs. oxaliplatin for peritoneal carcinomatosis arising from colorectal carcinoma did not demonstrate that one chemotherapeutic agent is significantly better in terms of survival than the other [29]. An ongoing North American phase II randomized trial is studying toxicity profile of intraperitoneal oxaliplatin vs. MMC and time to progression in patients with peritoneal carcinomatosis from appendiceal tumors (NCT01580410).
- A systematic review on CRS + HIPEC for peritoneal carcinomatosis arising from colorectal cancer reported an overall morbidity from 22 to 76 % (mean 49 %), and mortality from 0 to 19 % (mean 3.6 %) related to the procedure [17].

Patient Selection for Surgery

Patient selection is essential for successful surgery. Patient factors, tumor biology, and extent of disease constitute main factors to consider for selection of patients. These are inclusion and exclusion criteria for treatment [24, 30–32], used at University of Toronto.

Inclusion	Exclusion
• Diagnosis of carcinomatosis from colorectal origin (resectable), appendiceal neoplasms or mesothelioma • Medically fit for surgery • Completely cytoreducible disease • Generally < 70 years old (relative)	• Other primaries (e.g., gastric, breast, cholangiocarcinoma, pancreas) • Poorly differentiated or signet ring histology (relative) • Malignant small bowel obstruction (relative) • Ureteric obstruction from tumor • Extraperitoneal metastases (relative) • Retroperitoneal lymphadenopathy • Progression on chemotherapy

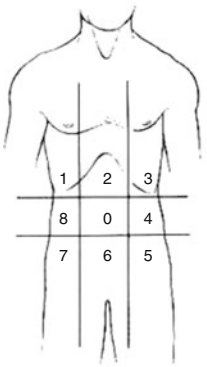
Special Notes

- Tumor biology plays an important role in evaluation of candidates for CRS + HIPEC. A better survival outcome after CRS + HIPEC is observed for tubulopapillary and epithelioid mesotheliomas and for DPAM/LAMN. Patients harboring poorly differentiated carcinoma from the appendix or colorectal have a lower median survival than those who have moderately differentiated tumor histology (17.7 vs. 41.3 months, respectively). For signet ring cell carcinomas, median survival is 7.2 vs. 29.4 months for those without signet ring cell feature [33]. Thus, high grade and signet ring cell histology are considered relative contraindications to CRS + HIPEC.
- A short disease-free interval (<12 months) between surgical treatment of the primary and development of peritoneal carcinomatosis, and tumor progression on systemic chemotherapy constitute poor prognostic features.

Assessment of Extent of Disease

- The peritoneal cancer index (PCI) is a score calculated intraoperatively indicating the extent of peritoneal disease. PCI represents one of the most significant prognostic factors, along with completeness of cytoreduction [34–36]. The PCI score is also used to estimate the likelihood of proceeding with cytoreduction, and to determine if the procedure is beneficial to the patient. The score is a summation of cancer lesions size (scored 0–3) present in the 13 abdominopelvic regions, with a maximum score of 39.
- CT and MRI are the most commonly used imaging modality to characterize peritoneal carcinomatosis. Sugarbaker has defined criteria on CT and MRI as predictors of unresectability: implant >5 cm in epigastrium, loss of normal architecture of small bowel, matted adjacent loops, segmental obstruction, distorted or thickened bowel, and inability to identify mesenteric vessels [37, 38]. However, conventional cross-sectional imaging can incorrectly estimate the degree of peritoneal disease by 20–30 %, making laparoscopy a useful tool for those patients [39].
- Diagnostic laparoscopy has been shown to be beneficial to evaluate the extent of disease and resectability [40]. Laparotomy may be superior to laparoscopy for visualizing the right hemidiaphragm, omental bursa, and pelvis, and remains the most accurate way to evaluate extent of PCI. Laparoscopy serves to determine PCI score more as a threshold to assess resectability than for accuracy and reduces the number of non-therapeutic laparotomies for patients found with extensive disease or without peritoneal carcinomatosis. Laparoscopy may also allow one to obtain tissue for diagnostic confirmation.
- A low PCI indicates a better probability of achieving complete cytoreduction, and is associated with better survival than a high PCI. With regard to PMCA, Sugarbaker reported that PCI ≤10 is associated with a 50 % 5-year survival; PCI of 11–20 with a 20 % 5-year survival and a PCI >20 with a 0 % 5-year survival [41]. Thus, a PCI <20 is recommended to perform CRS + HIPEC in these cases. For peritoneal carcinomatosis from colorectal origin, a similar threshold of PCI <20 is used to determine candidacy for CRS + HIPEC [14]. For patients with PMP from low grade mucinous appendiceal neoplasms, high PCI (>20) does not necessarily preclude CRS + HIPEC. CRS can thus be performed in one or two separate procedures, proceeding with the infra-mesocolic part first and the supra-mesocolic part done subsequently [24]. Well-differentiated papillary mesothelioma and multicystic subtypes have a high rate of cure with complete surgical resection. CRS + HIPEC are not warranted up front for these subtypes, and usually are reserved for mesothelioma recurrence or presence of extensive disease [42].

Peritoneal Cancer Index

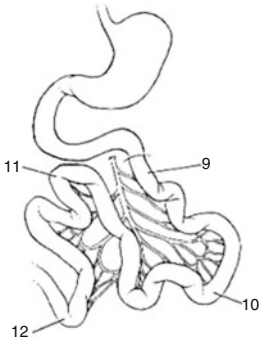


Regions		Lesion Size
0	Central	____
1	Right Upper	____
2	Epigastrium	____
3	Left Upper	____
4	Left Flank	____
5	Left Lower	____
6	Pelvis	____
7	Right Lower	____
8	Right Flank	____
9	Upper Jejunum	____
10	Lower Jejunum	____
11	Upper Ileum	____
12	Lower Ileum	____

PCI ☐

Lesion Size Score

LS 0 No tumor seen
LS 1 Tumor up to 0.5 cm
LS 2 Tumor up to 5.0 cm
LS 3 Tumor > 5.0 cm or confluence



- Once cytoreductive surgery is completed, evaluation of the amount of residual disease is performed using the completeness of cytoreduction score (CC-score). CC-score of 0 signifies no residual disease; CC-1 corresponds to deposits < 2.5 mm; CC-2 corresponds to deposits between 2.5 mm and 2.5 cm. Finally, CC-3 score corresponds to deposits > 2.5 cm.
- The Peritoneal Surface Disease Severity Score of colon cancer developed by Esquivel et al. may also be useful to determine resectability in carcinomatosis of colorectal origin, as it includes factors related to the patient, tumor histology, and extent of disease [25].
- Colonoscopy should be performed in patients with appendiceal mucinous neoplasms, as there is risk of finding a synchronous colorectal neoplasm.
- If thoracic imaging shows a pleural effusion, thoracentesis or video-assisted thoracic surgery (VATS) should be done for biopsy to rule out distant metastatic spread.

The next table summarizes the preoperative investigations, the surgical procedures, and the follow-up of these patients:

Workup	Cytoreduction surgery	HIPEC	Follow-up
• History and physical exam • Labs[a]: – Mesothelioma: CA-125 Mesothelin – LAMN/MACA: CA-19.9 CEA • Imaging: – CT abdomen/pelvis – CT chest • Colonoscopy (appendix and colorectal) • ±Diagnostic laparoscopy (evaluate extent of disease and resectability) • Path review • Discuss case in MCC	• Complete cytoreductive surgery (document PCI and decide if cytoreducible) • If cytoreducible: – Remove all visible disease CC-0/CC-1 resection – Selective peritonectomy – Omentectomy – Multivisceral resections if necessary – Resect previous port sites and scars or biopsy site if applicable	• Approaches: – Open Coliseum – Semi-closed[b] – Closed • Agents for mesothelioma: – Oxaliplatin[b] – MMC – Doxorubicin – Cisplatin • Agent for appendix: – MMC[b] • Agents for colorectal: – Oxaliplatin (concurrently used with IV 5FU-leucovorin)[b] – MMC	• Based on an international consensus statement • Every 3–4 months for 2 years, then every 6 months: – History and clinical exam – CA-125 + mesothelin if elevated pre-op in mesothelioma – CA-19.9, CEA, CA-125 if elevated pre-op in LAMN/MACA – CT of chest–abdomen–pelvis

MCC Multidisciplinary Cancer Conference, *MMC* mitomycin-C

[a]Can be followed for post-treatment surveillance [43–45]

[b]Used at the University of Toronto

Extraperitoneal Disease and Extensive Peritoneal Carcinomatosis

- The presence of synchronous liver metastases is a relative contraindication to performing CRS + HIPEC. In patients with synchronous peritoneal disease and liver metastases, overall survival is lower after CRS + HIPEC and liver resection than in patients without liver metastases (27 % vs. 66 %) [3]. However, selected patients with synchronous peritoneal disease and liver metastases may have improved overall survival after CRS + HIPEC and liver resection compared to treatment with systemic chemotherapy alone [46]. In a study by Maggiori et al., patients with a PCI <12 and three or fewer liver metastases achieved a median survival of 40 months [47]. Retroperitoneal lymphadenopathy and extra-abdominal metastases are generally viewed as absolute contraindications to CRS + HIPEC.
- The Canadian HIPEC Collaborative Group recommends different strategies for patients with extensive carcinomatosis. Closure of the abdomen with neoadjuvant systemic chemotherapy and reassessment for response to treatment can be undertaken. If significant tumor response, CRS + HIPEC can then be considered. For nonsurgical patient, a referral to medical oncology for systemic palliative chemotherapy should be discussed. Patients not candidate for chemotherapy should be referred for best supportive care [24].

Second Look Laparotomy and Prophylactic HIPEC

- Second look laparotomy may be useful to diagnose early peritoneal metastases that could not be diagnosed by imaging and clinical evaluation. Since PCI is the strongest predictor of outcome, this strategy has the potential advantage of identifying peritoneal carcinomatosis at a low burden with concomitantly improved survival. The population at highest risk of developing peritoneal carcinomatosis is: patient with perforated tumor, patient who underwent resection of limited peritoneal implants simultaneously with primary tumor and patient with ovarian metastases [48]. In a study by Elias et al., routine second look laparotomy was performed if metastatic work up was negative one year after diagnosis of cancer and six months after the end of systemic chemotherapy [3]. When macroscopic peritoneal carcinomatosis was found, Elias et al. performed CRS + HIPEC, resulting in a 2-year disease-free survival of 50 % [3].
- If no peritoneal carcinomatosis is found, prophylactic HIPEC may be undertaken. One French study reported a 17 % recurrence rate for patients with prophylactic HIPEC from colorectal cancer vs. 43 % for those without prophylactic HIPEC [49]. The Prodige 15 (ProphyloChip) study is a multicenter randomized trial comparing second look laparotomy followed by prophylactic HIPEC vs. observation alone for colorectal patients at high-risk of developing peritoneal carcinomatosis, with negative metastatic workup (NCT01226394). Accrual is in progress and the primary study endpoint is peritoneal recurrence rate at three years.

Recurrent Disease and Palliation

- There is very little data on how to treat patients with recurrence of peritoneal surface malignancy. In selected patients with a low PCI and good performance status, a repeat CRS + HIPEC may be performed. This was investigated by Brouquet et al. for a variety of histologies. With a mean PCI of 7.6 and a recurrence-free interval time of at least 12 months, 5 and 10 years actuarial survival rates were 72.5 % and 58 % respectively [50]. Prolonged survival of 12 months with a second complete CRS + HIPEC have been reported in other studies. However, the majority of those patients develop recurrence [51].
- For patients with symptomatic peritoneal disease that are not candidates for curative-intent surgery, repeat surgical debulking may offer palliation. Surgery can palliate obstructive symptoms due to peritoneal carcinomatosis in 32–100 % of cases. However, surgical treatment may also lead to prolonged time of hospitalization, significant complications (7–44 %), and recurrence of obstruction is reported to be as high as 47 % [52]. Patients and family must be fully informed of the potential benefits and risks of palliative surgery for obstructive disease related to peritoneal carcinomatosis. HIPEC can also be beneficial for the treatment of high volume malignant ascites in mesothelioma, even in the absence of complete cytoreduction (CC-2 resection).

Landmark Studies

Mesothelioma

There are no randomized controlled trials in peritoneal mesothelioma. The following are the most significant studies:

Study	Methods	Results
Yan et al. [22]	• Multi-institutional series • *N* = 405 • CRS • ±HIPEC Cisplatin + Doxorubicin; Cisplatin, Mitomycin C or both	• 46 % of patients had CC-0/CC-1 • 3 years-OS: 60 % • 5 years-OS: 47 %
Deraco et al. [53]	• Phase II Multi-institutional series • *N* = 61 • CRS • + HIPEC (C + D or C + MMC)	• 74 % of patients had CC-0/CC-1 • 5 years-OS: 54 %
Deraco et al. [54]	• Phase II Trial • *N* = 49 • CRS • + HIPEC (C + D or C + MMC)	• 88 % of patients had CC-0/CC-1 • 3 years-OS: 65 % • 5 years-OS: 57 %

(continued)

(continued)

Study	Methods	Results
Feldman et al. [31]	• Phase II Trial • *N* = 49 • CRS • HIPEC-Cisplatin • ± a single postoperative intraperitoneal dose of fluorouracil and paclitaxel between day 7 and 10	• 88 % of patients had CC-0/CC-1 • 1 year-OS: 86 % • 3 years-OS: 59 %

CRS cytoreductive surgery, *HIPEC* hyperthermic intraperitoneal chemotherapy, *C* cisplatin, *D* doxorubicin, *MMC* mitomycin C, *OS* overall survival

Appendix

There are no randomized controlled trials. The following are the most significant studies:

Study	Methods	Results
Sugarbaker et al. [41]	• Retrospective • *N* = 385 • DPAM + Intermediate PMCA • CRS + HIPEC (MMC) ± 5-FU post-op intraperitoneal for 5 days for PMCA	• DPAM 5-years OS: 86 % • Intermediate PMCA 5-years OS: 50 % • Incomplete CRS 5-years OS: 20 %
Youssef et al. [55]	• Retrospective • *N* = 456 • DPAM • CRS + HIPEC (MMC)	• 5-years OS: 69 % • 10-year OS: 57 %
Baratti et al. [32]	• Retrospective • *N* = 104 • DPAM/PMCA • CRS + HIPEC (MMC) + cisplatin	• CC-0/CC-1: 89 patients • 5-years OS: 78.3 %
Chua et al. [9]	• Multi-institutional retrospective • *N* = 2298 • DPAM + PMCA • CRS + HIPEC (or EPIC or both or none) (MMC or oxaliplatin or others)	• Median survival : 196 months (16.3 years) • Median PFS: 96 months (8.2 years) • 10-year OS: 63 % • 15-years OS: 59 % • Predictors of poorer OS: older age, PMCA subtype, CCR-2 or 3, prior chemotherapy tx, major post-operative complications

OS overall survival, *PFS* progression-free survival, *CRS* cytoreductive surgery, *MMC* mitomycin-C, *HIPEC* hyperthermic intraperitoneal chemotherapy, *DPAM* disseminated peritoneal adenomucinosis, *PMCA* peritoneal mucinous carcinomatosis, *EPIC*: early postoperative intraperitoneal chemotherapy

Colorectal

Study	Methods	Results
Verwaal et al. [12, 56]	• RCT • *N* = 105 • Colorectal and Appendiceal Adenocarcinomatosis (PMCA) • CRS + HIPEC (MMC) + systemic post-op 5-FU/LV vs. 5-FU/LV systemic chemo ± palliative surgery	• DSS: improved with CRS + HIPEC (43 vs. 23 months) • Median FU of 8 years: 45 % of patients in experimental arm who had CC-0 resection were still alive
Glehen et al. [15]	• Multi-institutional retrospective • *N* = 506 • Colorectal • CRS + HIPEC or EPIC (various agents)	• 1-year OS: 72 % • 3-years OS: 39 % • 5-years OS: 19 %
Elias et al. [13]	• Retrospective • *N* = 96 • Colorectal • CRS + HIPEC (Oxaliplatin) vs. Systemic (various regimens including Folfox, Folfiri, 5-FU)	• Improved OS with CRS + HIPEC • 2-years OS: 81 % vs. 65 % • 5-years OS: 51 % vs. 13 % • Age and tumor differentiation were not comparable in both groups
Elias et al. [14]	• Multi-institutional Retrospective • *N* = 523 • Colorectal • CRS + perioperative intraperitoneal chemotherapy HIPEC or EPIC (MMC or oxaliplatin)	• Median OS: 30.1 month • 5-years OS: 27 % • 5-years DFS: 10 %

EPIC early postoperative intraperitoneal chemotherapy, *RCT* randomized controlled trial, *CRS* cytoreductive surgery, *MMC* mitomycin-C, *PMCA* peritoneal mucinous carcinomatosis, *HIPEC* hyperthermic intraperitoneal chemotherapy, *DSS* disease-specific survival, *OS* overall survival, *DFS* disease-free survival

Referring to Medical Oncology

1. Systemic chemotherapy alone is an alternative treatment strategy for patients that are not surgical candidates.
2. The most common systemic chemotherapy used for peritoneal mesothelioma are pemetrexed ± cisplatin, carboplatin or gemcitabine [57, 58]. Another regimen used is cisplatin + irinotecan [59].
3. Multiple regimens have been used for carcinomatosis of appendiceal origin including 5-FU alone or in combination with oxaliplatin, irinotecan, ±bevacizumab or cetuximab [60]. A phase II trial with MMC and capecitabine showed a 38 % benefit in the form of stabilization or reduction of peritoneal disease [61]. A prospective trial of 34 patients receiving neoadjuvant FOLFOX showed 29 % of partial or complete responses [62].

4. Many trials have been performed to evaluate the best systemic treatment for metastatic colorectal cancer. These trials have included patients with carcinomatosis. A detailed discussion is beyond the scope of this chapter. Most regimens used include FOLFOX or FOLFIRI ± bevacizumab, cetuximab or panitumumab. The Combatac trial is an ongoing phase II study evaluating perioperative chemotherapy with oxaliplatin or irinotecan based regimen + cetuximab combined with CRS + HIPEC for wild-type KRAS peritoneal carcinomatosis from colorectal or appendiceal adenocarcinoma (NCT01540344) [63].
5. Neoadjuvant chemotherapy for high grade appendiceal malignancies and all peritoneal carcinomatosis from colorectal cancer should be considered prior to CRS + HIPEC.

Referring to Radiation Oncology

1. Radiation therapy is not indicated for peritoneal surface malignancies outside of clinical trials.

Referring to Multidisciplinary Cancer Conference (MCC)

1. All patients should be discussed.

Toronto Pearls

- When faced with an unexpected finding of peritoneal implants during elective or emergency surgery, abort elective surgery or treat emergency only. For colorectal cancer, biopsy of a peritoneal nodule is beneficial with an effort to preserve, as much as possible, the integrity of the peritoneal barrier and not hinder a future multimodality approach. In selected cases, minimal, localized, and completely resectable implants may be removed if included in the resection. For appendiceal tumors, the appendectomy should be performed if it is safe to do so for diagnostic purpose. Carefully document the PCI. Do a full investigation postoperatively with imaging, and refer the patient to a tertiary care center specialized in the treatment of peritoneal surface malignancies.
- Biopsies are ideally done under either CT-scan visual guidance or diagnostic laparoscopy, targeting the most high grade or suspicious looking lesion. Fine needle aspiration (FNA) and aspiration of intraperitoneal mucin for cytology is usually inadequate for diagnosis.
- Careful pathologic review by expert pathologist is essential to accurately diagnose peritoneal surface malignancies and their subtypes.

- Diagnostic laparoscopy is performed to evaluate the extent of disease in high grade mucinous adenocarcinoma of the appendix and peritoneal carcinomatosis from colorectal origin.
- If patients present with an acceptable PCI and have completely resectable disease: proceed to CRS + HIPEC. We use the semi-closed approach. For mesothelioma, we use oxaliplatin for 30 min, MMC for 90 min for low grade appendiceal cancers, and oxaliplatin (with IV 5FU + leucovorin given pre HIPEC) for 30 min, all at 43 °C (inflow temperature) for colorectal and high grade appendiceal adenocarcinomas. This may require multi-visceral resection and multiple anastomoses. CC-0/CC-1 resection is necessary to proceed with HIPEC, especially for colorectal cancer. However, in patients with mesothelioma, HIPEC may be considered to palliate malignant ascites in the absence of complete cytoreduction.
- For selected patients with colorectal and high grade appendiceal carcinomatosis, we recommend preoperative systemic chemotherapy for 6 months. This is performed to evaluate disease biology (progressive disease is generally a contraindication to CRS + HIPEC), to get a response in borderline disease, and to offer patients some degree of neoadjuvant chemotherapy, as they may not be fit for adjuvant chemotherapy within the first 3 months of surgery. Neoadjuvant chemotherapy is also used to treat potential microscopic distant disease.
- In patients that are not surgical candidates, chemotherapy alone may be the treatment of choice. We have seen some excellent clinical responses to systemic chemotherapy, including some patients who later become candidates for CRS + HIPEC.
- Due to possible late recurrences, extended follow-up is required.

References

1. McCusker ME, Coté TR, Clegg LX, et al. Primary malignant neoplasms of the appendix: a population-based study from the surveillance, epidemiology and end-results program, 1973–1998. Cancer. 2002;94:3307–12.
2. Rouzbahman M, Chetty R. Mucinous tumours of the appendix and ovary: an overview and evaluation of current practice. Postgrad Med J. 2015;91:41–5.
3. Elias D, Goere D, Dumont F, et al. Role of hyperthermic intraoperative peritoneal chemotherapy in the management of peritoneal metastases. Eur J Cancer. 2014;50:332–40.
4. Misdraji J. Mucinous epithelial neoplasms of the appendix and pseudomyxoma peritonei. Mod Pathol. 2015;28:S67–79.
5. Ronnett BM, Zahn CM, Kurman RJ, et al. Disseminated peritoneal adenomucinosis and peritoneal mucinous carcinomatosis. A clinicopathologic analysis of 109 cases with emphasis on distinguishing pathologic features, site of origin, prognosis, and relationship to "pseudomyxoma peritonei". Am J Surg Pathol. 1995;19:1390–408.
6. Ronnett BM, Yan H, Kurman RJ, et al. Patients with pseudomyxoma peritonei associated with disseminated peritoneal adenomucinosis have a significantly more favorable prognosis than patients with peritoneal mucinous carcinomatosis. Cancer. 2001;92:85–9.
7. Tang LH, Shia J, Soslow RA, et al. Pathologic classification and clinical behavior of the spectrum of goblet cell carcinoid tumors of the appendix. Am J Surg Pathol. 2008; 32(10):1429–43.

8. Edge SB, Byrd DR, Compton CC, et al. (Eds). AJCC (American Joint Committee on Cancer). Cancer staging manual. 7th ed. New York: Springer; 2010. p. 136–55.
9. Chua TC, Moran BJ, Sugarbaker PH, et al. Early and long-term outcome data of patients with pseudomyxoma peritonei from appendiceal origin treated by a strategy of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. J Clin Oncol. 2012;30:2449–56.
10. Sugarbaker PH. Epithelial appendiceal neoplasms. Cancer J. 2009;15(3):225–35.
11. Cao C, Yan TD, Black D, et al. A systematic review and meta-analysis of cytoreductive surgery with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis of colorectal origin. Ann Surg Oncol. 2009;16:2152–65.
12. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. J Clin Oncol. 2003;21:3737–43.
13. Elias D, Lefevre JH, Chevalier J, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27:681–5.
14. Elias D, Gilly F, Boutitie F, et al. Peritoneal colorectal carcinomatosis treated with surgery and perioperative intraperitoneal chemotherapy: retrospective analysis of 523 patients from a multicentric French study. J Clin Oncol. 2010;28:63–8.
15. Glehen O, Kwiatkowski F, Sugarbaker PH, et al. Cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for the management of peritoneal carcinomatosis from colorectal cancer: a multi-institutional study. J Clin Oncol. 2004;22:3284–92.
16. Elias D, Sideris L, Pocard M, et al. Efficacy of intraperitoneal chemohyperthemia with oxaliplatin in colorectal peritoneal carcinomatosis: preliminary results in 24 patients. Ann Oncol. 2004;15:781–5.
17. Nadler A, McCart JA, Govindarajan A. Peritoneal carcinomatosis from colon cancer: a systematic review of the data for cytoreduction and intraperitoneal chemotherapy. Clin Colon Rectal Surg. 2015 Dec;28(4):234–46.
18. Gervais MK, Dube P, McConnell Y, et al. Cytoreductive surgery plus hyperthemic intraperitoneal chemotherapy with oxaliplatin for peritoneal carcinomatosis arising from colorectal cancer. J Surg Oncol. 2013;108:438–43.
19. Mesothelioma and colorectal cancer. Canadian Cancer Society. http://www.cancer.ca/Canada-wide.aspx?sc_lang=en
20. Helm JH, Miura JT, Glenn JA, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: a systematic review and meta-analysis. Ann Surg Oncol. 2015;22(5):1686–93.
21. Yan TD, Deraco M, Elias D, et al. A novel tumor-node-metastasis (TNM) staging system of diffuse malignant peritoneal mesothelioma using outcome analysis of a multi-institutional database. Cancer. 2011;117(9):1855–63.
22. Yan TD, Deraco M, Baratti D, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. J Clin Oncol. 2009;27(36):6237–42.
23. Husain AN, Colby TV, Ordóñez NG, et al. Guidelines for pathologic diagnosis of malignant mesothelioma: 2012 update of the consensus statement from the International Mesothelioma Interest Group. Arch Pathol Lab Med. 2013;137:647–67.
24. Dube P, Sideris L, Law C, et al. Guidelines on the use of cytoreductive surgery and HIPEC in patients with peritoneal surface malignancy arising from colorectal or appendiceal neoplasms: From the Canadian HIPEC collaborative group. Curr Oncol. 2015;22(2):e100–12.
25. Esquivel J, Sugarbaker PH. Elective surgery in recurrent colon cancer with peritoneal seeding: when to and when not to proceed. G Chir. 1999;20:81–6.
26. Sugarbaker PH. Managing the peritoneal surface component of gastrointestinal cancer. Part 1. Patterns of dissemination and treatment options. Oncology (Williston Park). 2004;18:51–9.
27. Ceelen WP, Pahlman L, Mahteme H. Pharmacodynamic aspects of intraperitoneal cytotoxic therapy. Cancer Treat Res. 2007;134:195–214.

28. Elias D, Bonnay M, Puizillou JM, et al. Heated intra-operative intraperitoneal oxaliplatin after complete resection of peritoneal carcinomatosis: pharmacokinetics and tissue distribution. Ann Oncol. 2002;13:267–72.
29. Hompes D, D'Hoore A, Wolthuis A, et al. The use of oxaliplatin or mitomycin C in HIPEC treatment for peritoneal carcinomatosis from colorectal cancer: a comparative study. J Surg Oncol. 2014;109(6):527–32.
30. Yan TD, Brun EA, Cerruto CA, et al. Prognostic indicators for patients undergoing cytoreductive surgery and perioperative intraperitoneal chemotherapy for diffuse malignant peritoneal mesothelioma. Ann Surg Oncol. 2007;14:41–9.
31. Feldman AL, Libutti SK, Pingpank JF, et al. Analysis of factors associated with outcome in patients with malignant peritoneal mesothelioma undergoing surgical debulking and intraperitoneal chemotherapy. J Clin Oncol. 2003;21(24):4560–7.
32. Baratti D, Kusamura S, Nonaka D, et al. Pseudomyxoma peritonei: clinical pathological and biological prognostic factors in patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). Ann Surg Oncol. 2008;5:526–34.
33. Van Sweringen HL, Hanseman DJ, Ahmad SA, et al. Predictors of survival in patients with high-grade peritoneal metastases undergoing cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. Surgery. 2012;152:617–25.
34. Glehen O, Cotte E, Schreiber V, et al. Intraperitoneal chemohyperthermia and attempted cytoreductive surgery in patients with peritoneal carcinomatosis of colorectal origin. Br J Surg. 2004;91:747–54.
35. Koppe MJ, Boerman OC, Oyen WJ, Bleichrodt RP. Peritoneal carcinomatosis of colorectal origin: incidence and current treatment strategies. Ann Surg. 2006;243:212–22.
36. Pestieau SR, Sugarbaker PH. Treatment of primary colon cancer with peritoneal carcinomatosis: comparison of concomitant vs. delayed management. Dis Colon Rectum. 2000;43:1341–6.
37. Yan TD, Haveric N, Carmignani CP, et al. Abdominal computed tomography scans in the selection of patients with malignant peritoneal mesothelioma for comprehensive treatment with cytoreductive surgery and perioperative intraperitoneal chemotherapy. Cancer. 2005;103(4):839–49.
38. Low RN, Barone RM, Gurney JM, et al. Mucinous appendiceal neoplasms: preoperative MR staging and classification compared with surgical and histopathologic findings. Am J Roentgenol. 2008;190:656–65.
39. Jayakrishnan TT, Zacharias AJ, Sharma A, et al. Role of laparoscopy in patients with peritoneal metastases considered for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC). World J Surg Oncol. 2014;12:270–7.
40. Laterza B, Kusamura S, Baratti D, et al. Role of explorative laparoscopy to evaluate optimal candidates for cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with peritoneal mesothelioma. In Vivo. 2009;23(1):187–90.
41. Sugarbaker PH, Chang D. Results of treatment of 385 patients with peritoneal surface spread of appendiceal malignancy. Ann Surg Oncol. 1999;6:727–31.
42. Baratti D, Kusamura S, Nonaka D, et al. Multicystic and well-differentiated papillary peritoneal mesothelioma treated by surgical cytoreduction and hyperthermic intra-peritoneal chemotherapy (HIPEC). Ann Surg Oncol. 2007;14:2790.
43. Baratti D, Kusamura S, Martinetti A, et al. Circulating CA125 in patients with peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. Ann Surg Oncol. 2007;14(2):500–8.
44. Wheatley-Price P, Yang B, Patsios D, et al. Soluble mesothelin-related peptide and osteopontin as markers of response in malignant mesothelioma. J Clin Oncol. 2010;28(20):3316–22.
45. Van Ruth S, Hart AA, Bonfrer JM, et al. Prognostic value of baseline and serial carcinoembryonic antigen and carbohydrate antigen 19.9 measurements in patients with pseudomyxoma peritonei treated with cytoreduction and hyperthermic intraperitoneal chemotherapy. Ann Surg Oncol. 2002;9:961–7.

46. De Cuba EMV, Kwakman R, Knol DL, et al. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases; systematic review of all literature and meta-analysis of observational studies. Cancer Treat Rev. 2013;39:321–7.
47. Maggiori L, Goere D, Viana B, et al. Should patients with peritoneal carcinomatosis of colorectal origin with synchronous liver metastases be treated with a curative intent? A case control study. Ann Surg. 2013;258(1):116–21.
48. Honore C, Goere D, Souadka A, et al. Definition of patients presenting a high risk of developing peritoneal carcinomatosis after curative surgery for colorectal cancer: a systematic review. Ann Surg Oncol. 2013;20:183–92.
49. Elias D, Honore C, Dumont F, et al. Results of a systematic second-look surgery plus HIPEC in asymptomatic patients presenting a high risk of developing colorectal peritoneal carcinomatosis. Ann Surg. 2011;254:289–93.
50. Brouquet A, Goéré D, Lefèvre JH, et al. The second procedure combining complete cytoreductive surgery and intraperitoneal chemotherapy for isolated peritoneal recurrence: postoperative course and long-term outcome. Ann Surg Oncol. 2009;16(10):2744–51.
51. Klaver YL, Chua TC, Verwaal VJ, et al. Secondary cytoreductive surgery and peri-operative intraperitoneal chemotherapy for peritoneal recurrence of colorectal and appendiceal peritoneal carcinomatosis following prior primary cytoreduction. J Surg Oncol. 2013; 107(6):585–90.
52. Olson TJP, Pinkerton C, Brasel KJ, et al. Palliative surgery for malignant bowel obstruction from carcinomatosis, a systematic review. JAMA Surg. 2014;149(4):389–92.
53. Deraco M, De Simone M, Rossi CR, et al. An Italian Multicentric Phase II study on peritonectomy and intra peritoneal hyperthermic perfusion (IPHP) to treat patients with peritoneal mesothelioma. J Exp Clin Cancer Res. 2003;22:41–5.
54. Deraco M, Nonaka D, Baratti D, et al. Prognostic analysis of clinicopathologic factors in 49 patients with diffuse malignant peritoneal mesothelioma treated with cytoreductive surgery and intraperitoneal hyperthermic perfusion. Ann Surg Oncol. 2006;13:229–37.
55. Youssef H, Newman C, Chandrakumaran K, et al. Operative findings, early complications, and long-term survival in 456 patients with pseudomyxoma peritonei syndrome of appendiceal origin. Dis Colon Rectum. 2011;54:293–9.
56. Verwaal VJ, Bruin S, Boot H, et al. 8-year follow-up of randomized trial: cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy in patients with peritoneal carcinomatosis of colorectal cancer. Ann Surg Oncol. 2008;15:2426–32.
57. Carteni G, Manegold C, Garcia GM, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. Lung Cancer. 2009;64(2):211–8.
58. Simon GR, Verschraegen CF, Jänne PA, et al. Pemetrexed plus gemcitabine as first-line chemotherapy for patients with peritoneal mesothelioma: final report of a phase II trial. J Clin Oncol. 2008;26(21):3567–72.
59. Le DT, Deavers M, Hunt K, et al. Cisplatin and irinotecan (CPT-11) for peritoneal mesothelioma. Cancer Invest. 2003;21(5):682–9.
60. Shapiro JF, Chase JL, Wolff RA, et al. Modern systemic chemotherapy in surgically unresectable neoplasms of appendiceal origin: a single-institution experience. Cancer. 2010; 116:316–22.
61. Farquharson AL, Pranesh N, Witham G, et al. A phase II study evaluating the use of concurrent mitomycin C and capecitabine in patients with advanced unresectable pseudomyxoma peritonei. Br J Cancer. 2008;99:591–6.
62. Sugarbaker PH, Bijelic L, Chang D, Yoo D. Neoadjuvant FOLFOX chemotherapy in 34 consecutive patients with mucinous peritoneal carcinomatosis of appendiceal origin. J Surg Oncol. 2010;102:576–81.
63. Glockzin G, Rochon J, Arnold D, et al. A prospective multicenter phase II study evaluating multimodality treatment of patients with peritoneal carcinomatosis arising from appendiceal and colorectal cancer: the COMBATAC trial. BMC Cancer. 2013;13:67–77.

Chapter 21
Rectal Cancer

Andrea MacNeill, Shady Ashamalla, Marcus J. Burnstein, and Peter K. Stotland

Introduction

In 2014, an estimated 24,400 Canadians will be diagnosed with colorectal cancer and 9300 will die of the disease. Overall, colorectal cancer is the second leading cause of cancer death in men and the third most common cause of cancer death in women [1]. The death rate is declining in both sexes. Population-based screening has been shown to reduce mortality from colorectal cancer [2].

Presentation	Prognosis [3] 5-year overall survival (OS)
• Localized Disease (Stages I and II)	90 %
• Regional Disease (Stage III)	71 %
• Distant Metastasis (Stage IV)	13 %

The American Joint Committee on Cancer 7th edition is the current recommended Colorectal Cancer staging system.

In this chapter, the term rectal cancer refers to adenocarcinoma of the rectum, that is, adenocarcinoma arising at or above the anorectal junction (the pelvic floor) and at or below the rectosigmoid junction (where the taenia coli coalesce to form the confluent longitudinal muscle layer of the rectum).

A. MacNeill, M.D., M.Sc., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: andrea.macneill@mail.utoronto.ca

S. Ashamalla, M.D., M.Sc., F.R.C.S.C. • M.J. Burnstein, M.D., M.Sc., F.R.C.S.C.
P.K. Stotland, M.D., M.Sc., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: Shady.ashamalla@sunnybrook.ca; burnsteinm@smh.ca; peter.stotland@utoronto.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_21

Definitions/Terminology

- **Localized Rectal Cancer**: rectal adenocarcinoma without distant metastases, which can be divided into early (T1-2N0) and advanced (T3-4 any N) disease
- **Locally Advanced Rectal Cancer**: a non-specific term that encompasses a range of pathology from bulky T3 tumours to those requiring multivisceral resection
- **Transanal Excision (TAE)**: localized excision of a rectal lesion; in general, a full-thickness, intact, disc of the wall with a 1 cm mucosal margin
- **Transanal Minimally Invasive Surgery (TAMIS)/Transanal Endoscopic Microsurgery (TEM)**: transanal excision of a rectal lesion with the use of a specialized video operating system; these systems include the establishment of a pneumorectum and provide access to the middle and upper rectum
- **Total Mesorectal Excision (TME)**: excision of the rectum and the mesorectum in the plane between the visceral mesorectal fascia and parietal fascia
- **Low Anterior Resection (LAR)**: a sphincter-preserving TME with colorectal or coloanal anastomosis
- **Anterior Resection (AR)**: a tumour-specific mesorectal excision, dividing the mesorectum and rectum 5 cm below the distal extent of the lesion, at a right angle to the long axis of the rectum
- **Abdominoperineal Resection (APR)**: TME with en bloc excision of the anus
- Positive Margin: tumour cells extending to the cut edge of a specimen. In a TME specimen, a circumferential resection margin (CRM) of $\leq$1 mm is considered positive. Quirke et al. have identified six modes of margin involvement: [4]
  - Direct extension
  - Discontinuous tumour spread
  - Lymph node involvement
  - Venous invasion
  - Lymphatic invasion
  - Perineural spread

Management

Localized Rectal Cancer

<table>
<tr><th>Clinical scenario</th><th>Workup</th><th>Surgical management</th><th>Follow-up [5]</th></tr>
<tr><td>Early Rectal Cancer (T1-T2, N0)</td><td rowspan="2">• History and physical:
– Assessment of preoperative continence, sexual function, neurologic and vascular symptoms
– Family history (cancer syndromes)
– Emphasis on DRE
• Labs:
– CEA
• Colonoscopy
• Imaging:
– CT chest/abdo/pelvis
– Pelvic MRI
– Endorectal ultrasound (ERUS)</td><td>• Upper/Middle Rectum:
– LAR
• Lower Rectum:
– TME or APR
*Select T1 cancers with favourable features may be considered for local excision (TAMIS/TEM)</td><td rowspan="2">• History & physical, CEA q6 months × 5 years
• CT chest/abdo/pelvis yearly × 3 years
• Colonoscopy after 1 year, unless complete colonoscopy not performed preoperatively, in which case it should be done within 6 months. Frequency of surveillance colonoscopies to be determined by findings. If normal, repeat in 5 years</td></tr>
<tr><td>Locally Advanced Resectable Rectal Cancer (T3-T4, N0 or N+ disease)</td><td>• Upper/Middle Rectum:
– CRT followed by LAR
• Lower Rectum:
– CRT followed by TME or APR
*Multivisceral resection as required to obtain R0 resection</td></tr>
</table>

DRE digital rectal exam, *LAR* low anterior resection, *TAMIS* transanal minimally invasive surgery, *CRT* chemoradiotherapy, *APR* abdominoperineal resection, *ERUS* endorectal ultrasound

Special Notes

- The likelihood of synchronous colon carcinoma is 3–5 % and synchronous neoplasia is 10–20 %.
- ERUS is the most accurate imaging modality for differentiating T1 from T2 tumours, but MRI is superior for more advanced T stages, N stage, assessment of the circumferential resection margin and response to neoadjuvant therapy [6, 7].
- PET scan is a useful adjunct in assessing response to neoadjuvant CRT, and has been shown to be predictive of survival (OS and DFS). It can also identify distant disease, and distinguish local recurrence from postoperative change [8].

- Laparoscopic surgery for rectal cancer has been evaluated in a number of randomized controlled trials, and has been shown to have short-term benefits compared with open surgery. The risk of incomplete TME specimen is higher with open resection [9]. The COLOR II trial demonstrated significantly higher rates of positive CRM with open resection of low rectal cancers [10]. The COREAN trial reported equivalent oncologic outcomes at 3 years [11].
- APR is indicated for cancer invading or very closely encroaching upon the external anal sphincter. Compared to anterior resection, APR is associated with higher rates of specimen perforation, circumferential margin positivity and local recurrence, and lower overall survival [12–14]. An extra-levator perineal approach, which may be facilitated by the prone jack-knife position, provides a superior oncologic resection to conventional APR [15, 16].
- Neoadjuvant CRT has been shown to significantly decrease lymph node yield after resection for rectal cancer, with some evidence that this mirrors tumour regression in response to treatment [17, 18]. The relevance of the 12 lymph node benchmark in this context has been called into question [19].
- Pathologic tumour regression grade (TRG) is a measure of response to neoadjuvant therapy, based on degree of fibrosis and percentage viable cells. TRG is correlated with outcome, with a greater degree of regression predicting better survival. [20]. The College of American Pathologists classifies treatment effect according to the following schema: [21]

Description	Tumour regression grade
No viable cancer cells	0 (complete response)
Single cells or small groups of cancer cells	1 (moderate response)
Residual cancer outgrown by fibrosis	2 (minimal response)
Minimal or no tumour kill; extensive residual cancer	3 (poor response)

- An analogous classification of radiologic TRG based on pre- and post-neoadjuvant MRI has been shown to predict disease-free survival (DFS) and overall survival (OS) [22]. The degree of tumour regression on post-treatment MRI was more closely correlated with survival than T stage.

Special Considerations

Local Excision for Rectal Cancer

Traditional criteria for transanal excision (TAE) have been expanded with the evolution of TAMIS/TEM:

1. **Curative resection of low-risk T1 lesions** [23]
   - T1N0
   - Well differentiated
   - No lymphatic, vascular or perineural invasion
   - Less than 4 cm in width
   - Less than 50 % circumferential
   - Within 15 cm of anal verge
- At least 1 cm margin of normal tissue surrounding the tumour is required.
- Tumour fragmentation is associated with a higher incidence of local recurrence. [24]
- Immediate salvage resection is indicated for adverse pathologic findings. The evidence indicates that the oncologic outcomes of immediate salvage resection are equivalent to primary resection [25, 26]. However, there is concern that local excision renders subsequent salvage more technically challenging, and in some circumstances may preclude sphincter-sparing reconstruction [27, 28].

2. **Palliation of T2/T3 lesions**
- For local control in patients who cannot tolerate radical resection

3. **Confirmation of complete pathologic response following neoadjuvant CRT**
- Excision of scar following complete clinical response can confirm the absence of residual disease, potentially avoiding resection [29, 30] (see below). Phase 2 trials to determine the oncologic safety of this approach are ongoing [31].

Recommended Margins

- Proximal—minimum 5 cm (gross margins)
- Distal
  - Upper and Middle rectum—minimum 5 cm (gross margins in the rectal wall and in the mesorectum)
  - Lower rectum—ideally 2 cm[a] (gross margins)
- Circumferential Radial Margin—minimum 1 mm (microscopic margins) [32][b]

Chemoradiation in Rectal Cancer

- Extraperitoneal location of the rectum allows for radiotherapy with minimal toxicity to intra-abdominal structures (e.g. small bowel)
- Radiotherapy reduces local recurrence rate by 50 % [35, 36]
- Neoadjuvant RT or chemoradiation (CRT) is indicated for T3-4 lesions, any N+, or threatened circumferential radial margin
- The MERCURY study identified a subset of patients based on MRI staging who have a favourable prognosis with surgery alone, allowing omission of RT [37, 38]. These good prognosis features include: CRM >1 mm, no evidence of extramural venous invasion, T1-T3 any N. The results are currently being validated in prospective RCTs, including a phase 2 pan-Canadian trial

Neoadjuvant vs. Adjuvant Chemoradiation [39–41]

• Advantages of neoadjuvant therapy: – Significantly lower local recurrence rate, no difference in overall survival – Possibility of tumour downstaging, down-sizing, and possibly increased rate of sphincter preservation – Lower rates of acute and chronic toxicity – Lower rate of anastomotic stricture – Higher treatment completion rate	• Disadvantage of neoadjuvant therapy: – Overtreatment of some patients

(continued)

(continued)

Short- vs. Long-Course Radiotherapy [42, 43]
• Short-course RT = 25 Gy in 5 fractions followed by surgery in 1 week • Long-course CRT = 50.4 Gy in 28 fractions + 5FU followed by surgery in 8–12 weeks • No difference in overall survival, disease-free survival, local recurrence, or APR rates • Higher rate of pathologic downstaging with long-course CRT, including more complete pathologic responses • More acute toxicity with long-course CRT [44, 45] • Long-course CRT is standard of care in many North American centres, whereas short-course RT is widely practised in Europe
Complete Clinical Response After Neoadjuvant CRT
• Complete clinical response (cCR) to neoadjuvant CRT is associated with better outcome • cCR rates of 16–27 % reported in case series [46] • Limited data support a watchful waiting approach over radical resection in select cCRs: – Dutch study reports 2y OS 100 % and DFS 89 % in nonoperatively managed cohort [47] – Habr-Gama et al. report 94 % local control rate with watchful waiting approach, advocate close surveillance with immediate salvage in event of local recurrence [48] • Conflicting results from other centres indicate need for larger, prospective studies [49] • Promising case series suggest that local excision after cCR may be adequate [50, 51] • Radical resection remains the standard of care

[a]For low rectal tumours, a distal resection margin of 1 cm can be accepted to allow sphincter preservation. With appropriate technique and neoadjuvant therapy, a 1 cm margin is associated with rates of local recurrence and survival that are equivalent to wider margins [33].
[b]A positive CRM significantly increases the risk of local recurrence and is associated with decreased survival. In multivariate analyses, it has been identified as the single most important prognostic factor for local recurrence [34]

Locally Advanced Rectal Cancer (LARC) and Locally Recurrent Rectal Cancer (LRRC)

Workup	Perioperative treatment	Surgery
• History and physical: – Focus on urinary, gynecologic, neurologic symptoms, pain, lymphadenopathy • Labs: – CEA • Imaging: – CT chest/abdo/pelvis – MRI pelvis – PET or PET/CT—has been reported to change the management plan in 14 % of cases [52]	• Neoadjuvant CRT in primary disease • Evaluate for re-irradiation in previously irradiated pelvis [53] • Consider intraoperative radiotherapy if available and applicable [54] • Due to the high rate of distant failure, adjuvant systemic therapy is indicated	• En bloc resection of all involved structures to achieve an R0 resection margin [55, 56] • Early involvement of other surgical subspecialties (e.g. Urology, Orthopedics, Vascular)

CRT Chemoradiotherapy

Patterns of recurrence [57]	
Site	Comments
• Anastomotic recurrence • Inferior/perineal recurrence • Central recurrence (involving the rectum or urogenital structures)	• Amenable to resection
• Posterior recurrence	• Amenable to salvage resection when sacral involvement at or below S2
• Lateral recurrence	• May preclude resection with negative margins due to involvement of bony pelvis, major blood vessels and other lateral structures
Criteria for Unresectability [43]	
• Anatomic Involvement: – Above S2 or sacral ala – Acetabular involvement – Common or external iliac artery (relative) – Sciatic nerve or sciatic notch (relative) – Bilateral hydronephrosis (relative) • Biologic Factors: – Unresectable metastatic disease – Para-aortic lymph node involvement	• Patient Factors: – Refusal – Poor performance status – Unacceptable surgical risk • Technical Factors: – Inability to obtain a negative margin

Distant Metastatic Disease (Stage IV)

In patients with unresectable metastases, the median survival without systemic chemotherapy is 6–9 months. The addition of 5-fluorouracil (5-FU) based regimens improves survival to 12 months. Adding irinotecan or oxaliplatin to 5-FU extends survival to 20 months. More recently, with the identification of molecular targets and development of biologic agents, median survival has exceeded 30 months [58].

Workup	Surgery (referral to appropriate surgical subspecialty)	Follow-up
• History and physical • Labs: – CEA • Imaging: – CT chest/abdo/pelvis – MRI liver as indicated – US if ovarian metastases suspected – CT head/bone scan for symptoms – Consider PET/PET-CT to evaluate limited metastatic disease prior to planned resection [59]	• Liver: – Complete surgical resection with modern chemotherapy offers a 5-year overall survival up to 58 % [60–62] • Lung: – Complete surgical resection with modern chemotherapy offers a 5-year overall survival up to 55 % [63–65] • Peritoneum: – Cytoreductive surgery and HIPEC for colorectal metastases has a 5-year overall survival of 22–49 % [66] • Ovary: – Prophylactic oophorectomy is not routinely indicated, but bilateral oophorectomy is indicated if one ovary is involved • Brain: – Palliative resection may be indicated for carefully selected limited metastatic disease [67] • Bone: – Palliative radiotherapy	• Patients with potentially resectable disease undergoing chemotherapy should have imaging every 3 cycles to assess response • Monitor for toxicity depending on chemotherapeutic regimen used • CEA should be done only if patients do not have measurable disease on imaging • Patients undergoing palliation should only have blood tests and/or imaging as dictated by clinical condition

Special Notes

- In synchronous stage IV colorectal cancer, resection of the primary tumour has traditionally been discouraged in the absence of symptoms (e.g. bleeding, obstruction, perforation). This is based on the low proportion of asymptomatic primary tumours that progress to require intervention and the need for urgent systemic therapy in this population [68]. However, recent data question this dogma by demonstrating a survival advantage with resection of the primary in synchronous stage IV disease [69]. A prospective RCT is underway to help clarify the debate [70].

Landmark Trials

Study	Methods	Results
Heald et al. [71]	• Retrospective Review • *N* = 113 • Examination of Local Recurrence after TME	• LR = 0 % at 2 years with TME
Dutch Colorectal Cancer Group Trial Kapiteijn et al. [72]	• RCT • *N* = 1861 • Pre-op RT and TME vs. TME only	• LR: 2.4 % with pre-op RT and TME vs. 8.2 % TME only
Swedish Rectal Cancer Trial Gastrointestinal Tumour Study Group [23] Birgisson et al. [24]	• RCT • *N* = 1168 • Comparing pre-op RT and surgery vs. surgery alone	• LR: • 5 years: 11 % with pre-op RT vs. 27 % with surgery alone • 13 years: 9 % with pre-op RT vs. 26 % with surgery alone • OS: • 5 years: 58 % with pre-op RT vs. 48 % with surgery alone • 13-years: 38 % with pre-op RT vs. 30 % with surgery alone
German Rectal Cancer Trial Sauer et al. [25]	• RCT • *N* = 823 • Pre-op CRT vs. Post-op CRT	• LR: 6 % pre-op CRT vs. 13 % post-op CRT • No difference in 5-, 10-year OS • Toxicity (Grade 3/4): 27 % pre-op vs. 40 % post-op
NSABP R-03 Roh et al. [27]	• RCT • *N* = 267 • Pre-op CRT vs. Post-op CRT	• LR: 11 % in both arms
Polish Trial Bujko et al. [28]	• RCT • *N* = 316 • Pre-op CRT vs. short-course RT	• No difference in LR, DFS, sphincter preservation • Higher rate of pCR with pre-op CRT (16 % vs. 1 %) • Higher acute toxicity with pre-op CRT (18 % vs. 3 %)
Trans-Tasman Radiation Oncology Group (TROG) Trial Ngan et al. [29]	• RCT • *N* = 326 • Pre-op CRT vs. short-course RT	• No difference in LR, DFS, OS, sphincter preservation • Higher rate of pCR with pre-op CRT (15 % vs. 1 %)

(continued)

(continued)

Study	Methods	Results
MERCURY study Taylor et al. [37]	• Prospective observational study • *N* = 122 • Surgery alone for "good prognosis" stage I, II, and III disease based on MRI, no pre-op or post-op RT	• Similar rates of LR, DFS, OS compared to other studies involving RT

RCT randomized controlled trial, *TME* total mesorectal excision, *CRT* chemoradiotherapy, *RT* radiotherapy, *LR* local recurrence, *CRM* circumferential radial margin, *OS* overall survival

Referring to Medical Oncology

1. ≥T3
2. ≥N1
3. Recurrent rectal cancer
4. Metastatic disease

Referring to Radiation Oncology

1. ≥T3
2. ≥N1
3. Recurrent rectal cancer
4. Ambiguous T staging (T2/T3) and suspected close circumferential margin
5. T1/T2 tumours if:
   (a) There is residual tumour or fragmentation after local excision
   (b) There are adverse features on final pathology of local excision

Referring to Multidisciplinary Cancer Conference (MCC)

Other indications not mentioned above:

1. Stage IV disease to assess treatment versus palliation
2. Patients with underlying inflammatory bowel disease and patients with documented or suspect familial cancer syndromes
3. Patients with significant medical co-morbidities that may preclude optimal treatment plans

Toronto Pearls

- There is strong evidence, including RCTs, that placing a loop ileostomy at LAR decreases clinical leak rates and re-operation rates [73]. This is advised for anastomoses within 3–4 cm of the pelvic floor
- The rate of anastomotic leak after LAR is most consistently associated with the level of the anastomosis. Achieving a tension-free anastomosis to the distal rectum or anus is facilitated by ligation of the IMA at its origin and separate ligation of the IMV at the inferior border of the pancreas
- A 5–6 cm colonic J pouch for patients undergoing LAR ameliorates the functional disturbance known as Low Anterior Resection Syndrome
- In pelvic exenteration, early ligation of the internal iliac vessels facilitates hemostasis
- When a vertical rectus abdominis myocutaneous (VRAM) flap is needed for reconstruction of the perineum, it is advised to take it ipsilateral to the ileoconduit, rather than the colostomy to avoid colostomy prolapse
- If a surgeon encounters an unexpected locally advanced rectal cancer in a curable patient and is not prepared to perform appropriate multivisceral resection, the procedure should be aborted, after possible creation of a stoma, and the patient referred for multidisciplinary consultation
- In the dissection of anterior rectal tumours, or in the event of a threatened CRM, Denonvillier's fascia should be taken with the rectum. Otherwise, it should be left intact in order to preserve autonomic nerve function

References

1. Canadian Cancer Society, Statistics Canada. Canadian Cancer Statistics 2014
2. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med. 2009;150(1):1–8.
3. Howlader N, Noone AM, Krapcho M, et al (eds). SEER Cancer Statistics Review, 1975-2011, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2011/, based on November 2013 SEER data submission, posted to the SEER web site, April 2014. Accessed 28 Nov 2014.
4. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? J Clin Oncol. 2008;26(2):303.
5. Earle C, Annis R, Sussman J, et al. Follow-up care, surveillance protocol and secondary prevention measures for survivors of colon cancer. Toronto (ON): Cancer Care Ontario, 2012 Feb 3. Program in Evidence-Based Care Evidence-Based Series No.: 26-2.
6. Bipat S, Glas AS, Slors FJ, et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. Radiology. 2004; 232(3):773.
7. Al-Sukhni E, Milot L, Fruitman M, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2012;19(7): 2212–23.

8. Memon S, Lynch AC, Akhurst T, et al. Systematic review of FDG-PET prediction of complete pathological response and survival in rectal cancer. Ann Surg Oncol. 2014;21(11):3598–607.
9. Sajid MS, Ahamd A, Miles WFA, et al. Systematic review of oncological outcomes following laparoscopic vs open total mesorectal excision. World J Gastrointest Endosc. 2014;6(5): 209–19.
10. van der Pas M, Haglind E, Cuesta MA, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomized, phase 3 trial. Lancet Oncol. 2013;14(3):210–8.
11. Jeong SY, Park JW, Nam BH, et al. Open versus laparoscopic surgery for mid-rectal or low-rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): survival outcomes of an open-label, non-inferiority, randomized controlled trial. Lancet Oncol. 2014;15(7):767–74.
12. Marr R, Birbeck K, Garvican J, et al. The modern abdominoperineal excision: the next challenge after total mesorectal excision. Ann Surg. 2005;242:74–82.
13. Nagtegaal D, van de Velde C, Marijnen CAM, et al. Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol. 2005;23:9257–64.
14. Wibe A, Syse A, Andersen E, et al. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs abdominoperineal resection. Dis Colon Rectum. 2004;47:48–58.
15. Han JG, Wang ZJ, Wei GH, et al. Randomized clinical trial of conventional versus cylindrical abdominoperineal resection for locally advanced lower rectal cancer. Am J Surg. 2012;204(3):274–82.
16. West NP, Finan PJ, Anderin C, et al. Evidence of the oncologic superiority of cylindrical abdominoperineal excision for low rectal cancer. J Clin Oncol. 2008;26(21):3517.
17. Persiani R, Biondi A, Gambacorta MA, et al. Prognostic implications of the lymph node count after neoadjuvant treatment for rectal cancer. Br J Surg. 2014;101(2):133–42.
18. Awwad GE, Tou SI, Rieger NA. Prognostic significance of lymph node yield after long-course preoperative radiotherapy in patients with rectal cancer: a systematic review. Colorectal Dis. 2013;15(4):394–403.
19. Miller ED, Robb BW, Cummings OW, et al. The effects of preoperative chemoradiotherapy on lymph node sampling in rectal cancer. Dis Colon Rectum. 2012;55(9):1002–7.
20. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. J Clin Oncol. 2014;32(15):1554.
21. Protocol for the Examinatino of Specimens from Patients with Primary Carcinoma of the Colon. http://www.cap.org/apps/docs/committees/cancer/cancer_protocols/2011/Colon_11protocol.pdf Protocol web posting date: February 1, 2011. Accessed 28 Nov 2014.
22. Patel UBP, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. J Clin Oncol. 2011;29(28):3753–60.
23. Heidary B, Phang TP, Raval MJ, et al. Transanal endoscopic microsurgery: a review. Can J Surg. 2014;57(2):127–38.
24. Bouvet M, Milas M, Giacco GG, et al. Predictors of recurrence after local excision and postoperative chemoradiation therapy of adenocarcinoma of the rectum. Ann Surg Oncol. 1999;6:26–32.
25. Hahnloser D, Wolff BG, Larson DW, et al. Immediate radical resection after local excision of rectal cancer: an oncologic compromise? Dis Colon Rectum. 2005;48:429–37.
26. Levic K, Bulut O, Hesselfeldt P, et al. The outcome of rectal cancer after early salvage TME following TEM compared with primary TME: a case-matched study. Tech Coloproctol. 2013;17(4):397–403.
27. Bujko K, Richter P, Kolodziejczyk M, et al. Preoperative radiotherapy and local excision of rectal cancer with immediate radical re-operation for poor responders. Radiother Oncol. 2009;92(2):195–201.

28. Habr-Gama A, Sao Juliao GP, Perez RO. Pitfalls of transanal endoscopic microsurgery for rectal cancer following neoadjuvant chemoradiation therapy. Minim Invasive Ther. 2014;23(2):63–9.
29. Guerrieri M, Baldarelli M, Rimini M, et al. Transanal endoscopic microsurgery for rectal tumors: an option to radical surgery? Minerva Chir. 2013;68(3):289–98.
30. Perez RO, Habr-Gama A, Lynn PB, et al. Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum. 2013;56(1):6–13.
31. Pucciarelli S, De Paoli A, Guerrieri M, et al. Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum. 2013;56(12):1349–56.
32. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in local recurrence of rectal cancer. Lancet. 1994;344:707–11.
33. Fitzgerald TL, Brinkley J, Zervos EE. Pushing the envelope beyond a centimeter in rectal cancer: oncologic implications of close, but negative margins. J Am Coll Surg. 2011;213(5):589–95.
34. Nagtegaal ID, Gosens MJ, Marijnen CA, et al. Combinations of tumor and treatment parameters are more discriminative for prognosis than the present TNM system in rectal cancer. J Clin Oncol. 2007;25:1647–50.
35. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997, 336(14):980–7.
36. Folkesson J, Birgisson H, Pahlman L, et al. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol. 2005;23(24):5644–50.
37. Taylor FGM, Quirke P, Heald RJ, et al. Preoperative high-resolution magnetic resonance imaging can identify good prognosis stage I, II, and III rectal cancer best managed by surgery alone. Ann Surg. 2011;253(4):711–9.
38. Taylor FGM, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. J Clin Oncol. 2014;32(1):34–43.
39. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004;351(17):1731–40.
40. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. J Clin Oncol. 2012;30(16):1926–33.
41. Roh MS, Colangelo LH, O'Connell MJ. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. J Clin Oncol. 2009;27(31):5124–30.
42. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg. 2006;93:1215–23.
43. Ngan S, Fisher R, Goldstein D, et al. A randomized trial comparing local recurrence (LR) rates between short-course (SC) and long-course (LC) preoperative radiotherapy (RT) for clinical T3 rectal cancer: an intergroup trial (TROG, AGITG, CSSANZ, RACS). J Clin Oncol. 2010;28:15s.
44. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. EORTC Radiotherapy Group Trial 22921. N Engl J Med. 2006;355(11):1114.
45. McCarthy K, Pearson K, Fulton R, et al. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev. 2012;12, CD008368.
46. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg. 2012;99(7):918.
47. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011;29(35):4633.

48. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004;240(4):711.
49. Glynne-Jones R, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. Br J Surg. 2012;99(7):897.
50. Callender GG, Das P, Rodriguez-Bigas MA, et al. Local excision after preoperative chemoradiation results in an equivalent outcome to total mesorectal excision in selected patients with T3 rectal cancer. Ann Surg Oncol. 2010;17(2):441.
51. Borschitz T, Wachtlin D, Möhler M, et al. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol. 2008;15(3):712.
52. Faneyte IF, Dresen RC, Edelbrok MA, et al. Preoperative staging with positron emission tomography in patients with pelvic recurrence of rectal cancer. Dig Surg. 2008;25:202–7.
53. Das P, Delclos ME, Skibber JM, et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior irradiation. Int J Radiat Oncol Biol Phys. 2010;77:60–5.
54. Hyngstrom JR, Tzeng CW, Beddar S, et al. Intraoperative radiation therapy for locally advanced primary and recurrent colorectal cancer: ten-year institutional experience. J Surg Oncol. 2014;109(7):652–8.
55. Lehnert T, Methner M, Pollok A, et al. Multivisceral resection for locally advanced primary colon and rectal cancer. An analysis of prognostic factors in 201 patients. Anal Surg. 2002;235:217–35.
56. Bhangu A, Ali SM, Darzi A, et al. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. Colorectal Dis. 2012;14(12):1457–66.
57. Rodriguez-Bigas M, Chang C, Skibber J. Multidisciplinary approach to recurrent/unresectable rectal cancer: how to prepare for the extent of resection. Surg Oncol Clin N Am. 2010;19: 847–59.
58. Sridharan M, Hubbard JM, Grothey A. Colorectal cancer: how emerging molecular understanding affects treatment decisions. Oncology. 2014;28(2):110–8.
59. Culverwell AD, Chowdhury FU, Scarsbrook AF. Optimizing the role of FDG PET-CT for potentially operable metastatic colorectal cancer. Abdom Imaging. 2012;37(6):1021–31.
60. Choti MA, Sitzmann JV, Tiburi MF, et al. Trends in long-term survival following liver resection for hepatic colorectal metastases. Ann Surg. 2002;235(6):759–66.
61. Abdalla EK, Vauthey JN. Ellis LM, et al Recurrence and outcomes following hepatic resection, radiofrequency ablation, and combined resection/ablation for colorectal liver metastases. Ann Surg. 2004;239(6):818–25.
62. Fernandez FG, Drebin JA, Linehan DC, et al. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004;240(3):438–47.
63. Kanzaki R, Higashiyama M, Oda K, et al. Outcome of surgical resection for recurrent pulmonary metastasis from colorectal carcinoma. Am J Surg. 2011;202(4):419–26.
64. Blackmon SH, Stephens EH, Correa AM, et al. Predictors of recurrent pulmonary metastases and survival after pulmonary metastasectomy for colorectal cancer. Ann Thorac Surg. 2012; 94(6):1802.
65. Iida T, Nomori H, Shiba M, Metastatic Lung Tumor Study Group of Japan, et al. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: a retrospective analysis. Ann Surg. 2013;257(6):1059.
66. Yan TD, Black D, Savady R, et al. Systematic review on the efficacy of cytoreductive surgery combined with perioperative intraperitoneal chemotherapy for peritoneal carcinomatosis from colorectal carcinoma. J Clin Oncol. 2006;24(24):4011.
67. Lemke J, Scheele J, Kapapa T, et al. Brain metastases in gastrointestinal cancers: is there a role for surgery? Int J Mol Sci. 2014;15(9):16816–30.
68. Poultsides GA, Servais EL, Saltz LB, et al. Outcome of primary tumor in patients with synchronous stage IV colorectal cancer receiving combination chemotherapy without surgery as initial treatment. J Clin Oncol. 2009;27:3379–84.

69. Tarantino I, Warschkow R, Worni M, et al. Prognostic relevance of palliative primary tumor removal in 37,793 metastatic colorectal cancer patients. Ann Surg. 2015;262(1):112–20.
70. Rahbari NN, Lordick F, Fink C, et al. Resection of the primary tumour versus no resection prior to systemic therapy in patients with colon cancer and synchronous unresectable metastases (UICC stage IV): SYNCHRONOUS—a randomized controlled multicenter trial (ISRCTN30964555). BMC Cancer. 2012;12:142.
71. Heald RJ, Husband EM, Ryall RD. The mesorectum in rectal cancer surgery: the clue to pelvic recurrence? Br J Surg. 1982;69:613–6.
72. Kapiteijn E, Marijen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001;345:638–46.
73. Tan WS, Tang CL, Shi L, et al. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg. 2009;96(5):462–72.

Chapter 22
Retroperitoneal and Extremity Soft Tissue Sarcomas

Andrea MacNeill, Charles Catton, Brendan Dickson, Peter C. Ferguson, Rebecca A. Gladdy, and Abha Gupta

Introduction

Soft tissue sarcomas are rare malignant neoplasms that arise predominantly from mesenchymal tissues including fat, muscle, fibrous tissue, and blood vessels [1]. Although these are mostly sporadic cancers, there are several hereditary cancer syndromes such as Li–Fraumeni syndrome and Neurofibromatosis type 1 that are associated with sarcoma. Rarely, radiation-induced sarcomas can also arise as a late complication, often 10–15 years after treatment [2]. Approximately 1400 cases of sarcoma are diagnosed annually in Canada, representing nearly 1 % of all new cancers in adults and 12 % of all pediatric cancers [3]. This chapter addresses the workup and management of retroperitoneal and extremity soft tissue sarcoma. Gastrointestinal stromal tumors are covered elsewhere.

A. MacNeill, M.D., M.Sc., F.R.C.S.C.
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: andrea.macneill@mail.utoronto.ca

C. Catton, M.D., F.R.C.P.C.
Department of Radiation Oncology, University of Toronto, Toronto, ON, Canada
e-mail: charles.catton@rmp.uhn.on.ca

B. Dickson, M.D., M.Sc., F.C.A.P., F.R.C.P.C.
Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, ON, Canada
e-mail: bdickson@mtsinai.on.ca

P.C. Ferguson, M.D., F.R.C.S.C. • R.A. Gladdy, M.D., Ph.D., F.R.C.S.C., F.A.C.S. (✉)
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: PFerguson@mtsinai.on.ca; rgladdy@mtsinai.on.ca

A. Gupta, M.D., M.Sc., F.R.C.P.C.
Division of Medical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: abha.gupta@sickkids.ca

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_22

Disease site	Most common soft tissue subtypes [4]	Prognosis [5–8]	
		5 year overall survival (%)	5 year local recurrence (%)
Retroperitoneal (15 % of STS)	• Liposarcoma • Leiomyosarcoma • Fibrosarcoma • Malignant peripheral nerve sheath tumor (MPNST)	66–75	25–37
Extremity (45 % of STS)	• Liposarcoma • Undifferentiated/unclassified sarcoma[a] • Synovial sarcoma • Myxofibrosarcoma • Fibrosarcoma • Malignant peripheral nerve sheath tumor (MPNST)	68–80	5–15

STS soft tissue sarcoma, *MPNST* malignant peripheral nerve sheath tumor
[a]Previously known as malignant fibrous histiocytoma (MFH), also called sarcoma not otherwise specified (NOS), subdivided into spindle cell, round cell, pleomorphic, and epithelioid variants [9]

Tumor Biology

Type of disease recurrence	Most common subtypes
Local recurrence	• Retroperitoneal (20–50 % LRR): liposarcoma (especially dedifferentiated), MPNST, leiomyosarcoma • Extremity (5–15 % LRR): myxofibrosarcoma
Lung metastasis (30 %)	• Leiomyosarcoma • Rhabdomyosarcoma • MPNST • Ewing's sarcoma • Extraskeletal chondrosarcoma • Retroperitoneal dedifferentiated liposarcoma
Lymph nodes [10–12] (5 %)	• Rhabdomyosarcoma (10–32 %) • Epithelioid sarcoma (13–32 %) • Clear cell sarcoma (11–27 %) • Angiosarcoma (11–24 %) • Synovial sarcoma

(continued)

(continued)

Type of disease recurrence	Most common subtypes
Liver metastasis (5–10 %)	• Retroperitoneal leiomyosarcoma • Retroperitoneal dedifferentiated liposarcoma
Extrapulmonary metastasis (retroperitoneum, mediastinum, bone and soft tissue metastases) (10–15 %)	• Myxoid/round cell liposarcoma • Retroperitoneal leiomyosarcoma

MPNST malignant peripheral nerve sheath tumor, *LRR* local recurrence rate

Special Notes

- Sarcomas grow by direct local extension into adjacent tissues and structures, often pushing them aside and rarely violating major fascial planes, joints or bone. Lymph node involvement is rare, and typically seen with specific histologic subtypes (see table above) [13].
- The most important prognostic factors for systemic recurrence and overall survival are tumor grade, size, and depth, which are essential components of staging.
- The most important prognostic factors for local recurrence are anatomic site, use of radiation and R0 resection [14, 15].
- Retroperitoneal sarcomas tend to recur locally (first site of failure in 90 %), whereas extremity sarcomas more commonly recur distantly [16].
- Ten percent of patients have distant metastases at initial presentation, the majority of which are lung metastases [17].
- Lung metastases are most often associated with large, deep, high-grade sarcomas [18].
- The American Joint Committee on Cancer (AJCC) 7th edition is the current recommended sarcoma staging system. It incorporates histologic grade as well as TNM status. It is more applicable to extremity sarcomas than retroperitoneal tumors. The most significant change in the 7th edition is the downstaging of nodal disease from stage IV to stage III [19].
- An alternative staging system has been proposed for retroperitoneal sarcomas, incorporating histologic grade, completeness of resection, and presence of metastases. It has not been widely adopted [20].
- Nomograms have been developed and validated in order to more accurately predict postoperative survival, and are applicable to both retroperitoneal and extremity sarcomas, and also based on subtype [21, 22].

Management

Retroperitoneal Sarcoma Localized Disease

Workup	Neoadjuvant treatment	Surgery	Follow-up [23]
• History and physical exam – Include nodal basins and testicular exam • Labs[a]: – β-HCG – α-FP – LDH • Imaging: – CT abdo/pelvis + core biopsy – Differential renal scan if nephrectomy anticipated – CT chest for staging • Pathology review • Case discussion at MCC	• Consider neoadjuvant radiation or clinical trial if available • Consider neoadjuvant chemotherapy: – For chemosensitive tumors, such as RMS or Ewing's – For cytoreduction of borderline resectable tumors which may be chemosensitive, such as leiomyosarcoma and myxoid/round cell liposarcoma	• En bloc resection of tumor and closely associated viscera and retroperitoneal musculature/fat with a goal of complete R0 resection	• Low grade tumor—every 6 months for the first 2–3 years, then yearly: • History and physical exam • CT abdo/pelvis • High grade tumor—every 4 months for the first 2–3 years, then every 6 months for the next 2 years, then yearly: • History and physical exam • CT chest/abdo/pelvis

MCC multidisciplinary cancer conference, *RMS* rhabdomyosarcoma
[a]Tumor markers to rule out germ cell tumor, metastatic testicular carcinoma and lymphoma

Radiotherapy

- Both preoperative and postoperative radiotherapy are associated with reduced local recurrence rates in cohort studies (see Landmark Trials), but no level I data exist [24–26]
- An EORTC randomized phase III trial is currently investigating preoperative radiotherapy + surgery versus surgery alone [27]
- Preoperative radiotherapy is the preferred approach at the University of Toronto and other major sarcoma centers

Advantages of pre-op RT	**Disadvantages of pre-op RT**
• In situ tumor allows accurate targeting of radiation volume and precise delivery • Tumor displaces the radiosensitive viscera outside the treatment field, thereby limiting toxicity and allowing delivery of a higher dose • Radiation is theoretically more biologically effective preoperatively • May extend the surgical margin to reduce the risk of local recurrence	• Increased risk of wound healing complications • Possible increased risk of complications if vascular resection and reconstruction are required

Relative contraindications to RT

- Li–Fraumeni syndrome
- History of prior radiation
- Tumor crossing midline
- Solitary kidney
- Patient preference

Special Notes

- Sarcomas tend to be heterogeneous in morphology, and thus it is essential to ensure adequate sampling. Needle core biopsies are commonly used to diagnose abdominal sarcomas and a minimum of four large gauge cores are generally advised. In most cases this will provide sufficient tissue for histomorphologic assessment, routine immunohistochemical studies, as well as molecular analysis (both FISH and RT-PCR). All of these studies can be performed from formalin-fixed paraffin-embedded tissues. Cytologic assessment of soft tissue tumors by fine needle aspiration is not typically advised.
- Criteria for unresectability: diffuse metastases, peritoneal implants, extensive involvement of the SMA/SMV.
- Relative contraindications to resection: spinal cord involvement, vascular involvement (aorta, IVC, iliac vessels, porta hepatis). In select cases, vascular reconstruction can be undertaken.
- Resect all retroperitoneal fat in retroperitoneal liposarcomas.
- The most common organs removed en bloc with a retroperitoneal sarcoma are kidney, colon, spleen, pancreas, small bowel, diaphragm, psoas, and iliacus [28, 29].

Retroperitoneal Sarcoma: Locally Recurrent Disease

Workup	Neoadjuvant treatment	Surgery	Follow-up [17]
• History and physical exam • Labs: – No specific tests • Imaging: – CT abdo/pelvis ± core biopsy • CT chest for staging • Pathology review • Case discussion at MCC	• Neoadjuvant radiation if not previously irradiated • Consider high precision techniques (e.g., IMRT or intraoperative RT) if previously irradiated • Can also consider neoadjuvant chemo, especially if re-irradiation is not possible	• Resect if technically feasible without excessive morbidity, and no widespread metastases • Must be able to achieve complete resection. No role for debulking, except for palliation of symptoms in select circumstances [30]	• Low grade tumor—every 6 months for the first 2–3 years, then yearly: • History and physical exam • CT abdo/pelvis • High grade tumor—every 4 months for the first 2–3 years, then every 6 months for the next 2 years, then yearly: • History and physical exam • CT chest/abdo/pelvis

Special Notes

- Re-irradiation is often contraindicated, but this must be discussed in a tumor board with expert radiation oncologists specialized in sarcoma.
- Criteria for resectability similar to primary localized disease.

- Completely resected, low grade recurrences with growth rates of <0.9 cm/month have superior disease specific survival [31].
- Second and third recurrences become more challenging to resect, and with each recurrence survival diminishes while morbidity increases [5].
- An EORTC trial of adjuvant chemotherapy with regional hyperthermia showed some benefit in local control of recurrent or incompletely resected non-extremity sarcomas [32].

Retroperitoneal Sarcoma: Metastatic Disease

Considerations

- Management of metastatic soft tissue sarcoma is complex, and is best managed in the context of a multidisciplinary expert sarcoma center in order to establish appropriate goals of care, which may include either curative-intent resection or palliation.
- Palliative chemotherapy can slow disease progression, and possibly reduce tumor size to relieve symptoms, but data showing improved survival are lacking.
- Select patients with localized small volume metastases to the lung, liver or soft tissues in whom resection can be carried out with acceptable morbidity should be considered for metastasectomy.
- Five year overall survival up to 40 % has been reported after pulmonary metastasectomy [33–35].
- Very limited data exist regarding hepatic metastasectomy [36–38].

Workup	Management
• History and physical exam • Labs: – No specific tests • Imaging: – CT abdo/pelvis ± core biopsy • Case discussion at MCC	• Criteria for resectability: – Patient can medically tolerate the intervention and its physiologic consequences – The primary tumor is fully resected or resectable – Complete resection seems feasible – Tumor has favorable biology (slow growing, isolated/low-volume disease) – For lung: no extra-thoracic disease, pleural effusion or mediastinal/hilar adenopathy • Predictors of good outcome: – Complete R0 resection – Less than 50 years old – Interval between primary disease and metastasis greater than 12–18 months – Isolated/few metastases – Lung: tumor less than 2 cm – Liver: histology of LMS, GIST • Procedure: – Pulmonary wedge resection (open/VATS) – Partial hepatectomy

MCC multidisciplinary case conference, *R0* negative microscopic margins, *LMS* leiomyosarcoma, *GIST* gastrointestinal stromal tumor

Extremity Sarcoma: Localized Disease

Workup	Adjunctive treatment	Surgery	Follow-up [17]
• History and physical exam • Labs: – No specific tests • Imaging: – MRI + core biopsy or surgical biopsy – CT chest for staging – CT abdomen/pelvis in myxoid liposarcoma – CT of regional nodes in epithelioid sarcoma, rhabdomyosarcoma, clear cell sarcoma, angiosarcoma • Pathology review • Case discussion at MCC	• Neoadjuvant or adjuvant radiation • Neoadjuvant chemotherapy in patients with specific histologic subtypes (RMS, Ewing's sarcoma) or in other subtypes thought to be chemo sensitive (synovial sarcoma, high grade liposarcoma, leiomyosarcoma) to facilitate limb salvage in borderline resectable lesions	• Goal: complete (R0) resection with preservation of maximal function • Limb salvage is almost always possible • May require Plastic Surgery for advanced reconstruction	• Every 3 months for 2 years, then every 6 months for 3 years, then annually for 5 years: – History and physical exam – Chest X-ray • For high recurrence risk[a], MRI primary site every 4–6 months for 2 years, then yearly up to 5 years

[a]Positive margins or difficult area to examine (e.g., pelvis)

Special Notes

- If surgical biopsy is performed, care must be taken not to compromise definitive excision—longitudinal incision in the long axis of the limb, meticulous hemostasis, avoid mobilizing skin flaps and violating fascial planes.
- Resect outside the tumor pseudocapsule, excising a margin of normal tissue around the tumor. A 1–2 cm margin of uninvolved tissue is ideal, but often not feasible. A closer margin is acceptable if it includes a fascial plane.
- Pre-operative and post-operative radiation have similar local control rates. Pre-op radiation is associated with higher rates of acute wound healing complications, whereas post-op radiation entails higher rates of late, irreversible toxicities [39].
- Radiotherapy can be omitted in small (<5 cm), superficial, low-grade tumors resected with margins >1 cm [40].
- Primary amputation is indicated for extensive vascular/nerve involvement, infected tumor, anticipated poor soft tissue coverage and expected poor functional outcome with limb salvage. Primary amputation occurs in approximately 1 % of cases [41].
- Resection of the primary tumor in the setting of widespread metastatic disease requires multidisciplinary discussion; it may be considered for control of symptoms in patients with anticipated prolonged survival.

Historically, the treatment of extremity sarcoma was amputation. Limb salvage techniques ± radiation have proven equally effective. In a landmark trial comparing amputation vs. resection with adjuvant radiation, there was no difference in disease-free or overall survival [42]. Function is paramount when considering limb salvage. Major arteries and veins are preserved whenever possible, and preoperative radiation may sterilize the surgical field to allow preservation of structures. However, if needed, arteries can be resected and reconstructed, tendon transfers can restore function if major nerves must be sacrificed and veins can be reconstructed or simply ligated in order to achieve complete resection. Approximately 5 % of extremity sarcomas will metastasize to the lymph nodes, rendering lymphadenectomy unnecessary. Some exceptions, especially when nodes are clinically involved, include synovial sarcoma, angiosarcoma, rhabdomyosarcoma, epithelioid sarcoma and clear cell sarcoma [8].

Extremity Sarcoma: Locally Recurrent Disease

Workup	Adjunctive treatment	Surgery	Follow-up
• History and physical exam • Labs: – No specific tests • Imaging: – MRI ± core biopsy – CT chest • Path review • Case discussion at MCC	• Neoadjuvant radiation (or chemoradiation) if not previously irradiated • Consider high precision techniques (e.g., IMRT) if previously irradiated	• Limb-sparing re-resection • Amputation if limb salvage not feasible (10–25 %)	• Every 3 months for 2 years, then every 6 months for 3 years, then annually for 5 years: – History and physical exam – Chest X-ray or CT chest • For high recurrence risk[a], MRI primary site every 4–6 months for 2 years, then yearly up to 5 years

[a]Positive margins or difficult area to examine (e.g., pelvis)

Special Notes

- Five to 10 % of patients will recur even after complete resection and radiation therapy, usually within the first 2 years [43, 44].
- In Europe, isolated limb perfusion/infusion with TNF and melphalan has been studied with promising preliminary results [45].

Extremity Sarcoma: Lung Metastases

Workup	Management
• History and physical exam • Labs: – No specific tests • Imaging: – CT chest/abdo/pelvis • Case discussion at MCC	• Criteria for resectability: – Patient can medically tolerate the intervention and its physiologic consequences – The primary tumor is fully resected or resectable – Complete resection seems feasible – Tumor has favorable biology (slow growing, isolated/low-volume disease, long disease-free interval) – No extra-thoracic disease, pleural effusion, or mediastinal/hilar adenopathy • Predictors of good outcome: – Complete R0 resection – Less than 50 years old – Interval between primary disease and metastasis greater than 12–18 months – Isolated/few metastases – Tumor less than 2 cm – Three or fewer metastases/unilateral disease • Procedure: – Pulmonary wedge resection (open/VATS) • Consider palliative chemotherapy for growing or symptomatic lesions

Landmark Publications

Retroperitoneal Sarcoma

Study	Methods	Results
Sindelar et al. [46] (all grades of sarcoma)	• RCT • $N=35$ • IORT (20 Gy) + low dose (35–40 Gy) adjuvant EBRT vs. high dose adjuvant EBRT (50–55 Gy)	• No difference in median survival • With IORT: fewer local recurrences, less radiation enteritis, but higher radiation-induced peripheral neuropathy
Gieschen et al. [47] (all grades of sarcoma)	• Retrospective • $N=37$ • Neoadjuvant EBRT (45 Gy) + resection ± IOERT boost (10–20 Gy)	• With IOERT: improved OS and local control
Stoeckle et al. [18] (84 % intermediate-high grade)	• Retrospective • $N=165$ • Resection ± adjuvant EBRT (50 Gy)	• With EBRT: fewer local recurrences and improved recurrence-free survival

(continued)

(continued)

Smith et al. [48] (all grades of sarcoma)	• Prospective • $N=40$ • Neoadjuvant EBRT (45–50 Gy), + adjuvant BRT (20–25 Gy) in some patients • Median follow-up 106 months	• With pre-op EBRT: favorable long-term RFS and OS compared to historical controls. Post-op BRT was not associated with better disease control, resulted in unacceptable toxicity

RCT randomized controlled trial, *IORT* intraoperative radiation therapy, *OS* overall survival, *EBRT* external beam radiation therapy, *IOERT* intraoperative electron beam radiation, *BRT* brachytherapy, *DFS* disease-free survival

Extremity Sarcoma

Study	Design	Results
Rosenberg et al. [36] (high grade)	• RCT • $N=43$ • Amputation vs. limb-sparing surgery + adjuvant EBRT (50 Gy whole limb + 60–70 Gy boost to tumor bed) • Both groups received adjuvant chemo (doxorubicin, cyclophosphamide, high dose methotrexate)	• Higher local recurrence rate with limb salvage, but no difference in DFS or OS
Pisters et al. [49] (low and high grade)	• RCT • $N=164$ • Surgery ± adjuvant intraoperative BRT (42–45 Gy) delivered over 4–6 days	• With BRT: improved local control for high-grade sarcoma only • No difference in survival
Yang et al. [50] (low and high grade)	• RCT • $N=141$ • Limb-sparing surgery ± adjuvant EBRT (45 Gy wide field and 18 Gy boost tumor bed)	• With EBRT: decreased local recurrence • No difference in OS
O'Sullivan et al. [33] (all grades)	• RCT • $N=190$ • Neoadjuvant EBRT (50 Gy) vs. adjuvant EBRT (66 Gy)	• No difference in local control, DFS or OS • More grade 2–4 late toxicity with adjuvant EBRT

RCT randomized control trial, *EBRT* external beam radiation therapy, *OS* overall survival, *DFS* disease-free survival, *BRT* brachytherapy

Referring to Medical Oncology

1. Potentially chemosensitive tumors with borderline resectability, to allow for cytoreduction in a neoadjuvant approach (synovial sarcoma, high grade liposarcoma, leiomyosarcoma).
2. Ewing's sarcoma, rhabdomyosarcoma.
3. Metastatic disease for palliation.
4. Referral for phase 1 clinical trials for experimental agents.

Doxorubicin is the agent most commonly used in the treatment of soft tissue sarcoma (STS) and can be offered to patients with metastatic disease for palliation [51]. The opportunity to participate in available clinical trials should be offered to all patients with metastatic disease. Neoadjuvant combination therapy with doxorubicin plus ifosfamide can also be considered for patients with locally advanced, borderline resectable tumors in order to achieve cytoreduction and facilitate surgical resection. Certain subtypes, including synovial sarcoma and myxoid/round cell liposarcoma, are considered more sensitive than other histologies [52, 53]. In patients with resectable STS, several randomized controlled trials do not support the routine use of adjuvant chemotherapy [54–56]. Ewing's sarcoma and rhabdomyosarcoma are highly chemosensitive tumors. All patients with these tumors should receive multi-agent chemotherapy prior to surgery [57, 58].

The following drugs have been shown to have some activity in the following subtypes:

Histologic subtype	Suggested chemotherapy
Angiosarcoma	Taxane or pegylated liposomal doxorubicin
Leiomyosarcoma (mainly uterine)	Gemcitabine ± docetaxel
Rhabdomyosarcoma	Vincristine, dactinomycin, cyclophosphamide
Ewing's sarcoma	VDC ± ifosfamide and etoposide
All other histologies	Gemcitabine, pazopanib, doxorubicin ± ifosfamide

VDC vincristine, doxorubicin, cyclophosphamide

Referring to Radiation Oncology

1. All large, deep, retroperitoneal and extremity sarcomas in a neoadjuvant setting.
2. Extremity sarcomas where surgical margins are expected to be close, in order to preserve critical structures such as major nerves, vessels, or bone.
3. Extremity sarcomas with unexpectedly close margins, for consideration of adjuvant radiation.
4. Locally recurrent retroperitoneal and extremity sarcomas.
5. Palliation of symptomatic metastatic or locally recurrent unresectable retroperitoneal or extremity sarcoma.

Radiation therapy should be considered as part of multidisciplinary care in sarcoma. Unlike extremity sarcomas, the role of RT is not clearly established for RPS [18, 40, 41, 59]. The EORTC STRASS trial, a multicenter phase III randomized trial, is currently underway to compare neoadjuvant radiation plus surgery to surgery alone for retroperitoneal sarcomas, in an attempt to determine the effect of radiation on recurrence-free and overall survival.

With respect to extremity sarcoma, there are several randomized control trials showing that radiation decreases local recurrence [42, 43]. Radiation has also greatly improved the rate of limb salvage in extremity sarcoma. A landmark Canadian trial comparing neoadjuvant vs. adjuvant radiation therapy in patients with extremity sarcomas showed no difference in recurrence or survival, but more late high grade toxicities were seen with adjuvant radiation [33]. Another Canadian study evaluated re-irradiation for local recurrence, and found significantly better local control with this modality, leading them to conclude that excision with re-irradiation should be considered primary salvage therapy for local recurrence [60].

Referring to Multidisciplinary Cancer Conference (MCC)

All sarcoma cases should be discussed with a panel that routinely manages this disease.

Toronto Pearls

- In the event of an unexpected finding of a retroperitoneal mass during emergency surgery, treat the emergency and close. Investigate the lesion postoperatively with appropriate imaging and refer to a tertiary care center specialized in sarcoma.
- Image-guided biopsies are ideally undertaken at sarcoma centers with specialized radiologists and pathologists trained in their interpretation. Under visual guidance, the most high grade or suspicious looking portion of the lesion is targeted. A minimum of four large gauge core biopsies are required. Fine needle aspiration (FNA) is inadequate for diagnosis.
- Sample review by a pathologist with subspecialty expertise in sarcoma—and access to the requisite immunohistochemical and molecular diagnostic capabilities—is essential to accurately diagnose and characterize sarcoma.
- Detailed expert radiologic interpretation aids in defining the extent of disease and complex preoperative surgical planning.
- For intermediate or high-grade sarcoma, consider neoadjuvant radiotherapy, as this may result in tumor necrosis and possibly cytoreduction, as well as increase the likelihood of complete R0 resection. Radiation therapy is more accurately delivered to an in situ tumor, with less toxicity.
- Neoadjuvant single or multi-agent chemotherapy can be considered for patients with locally advanced borderline resectable tumors and favorable histology.

All patients with advanced (palliative or unresectable) sarcoma should be considered for clinical trials.

- Multi-visceral resection is usually required to achieve R0 resection in RP sarcoma.
- Retroperitoneal sarcoma patients must undergo lifelong surveillance, given the possibility of late recurrence.
- Excellent local control and functional outcomes can be achieved in extremity sarcoma with neoadjuvant radiotherapy and limb-sparing R0 resection.

References

1. Weiss SW, Goldblum J. General considerations. In: Weiss SW, editor. Enzinger and Weiss' soft tissue tumors. Philadelphia, PA: Saunders/Elsevier; 2013. p. 1.
2. Gladdy RA, Qin LX, Moraco N, et al. Do radiation-associated soft tissue sarcomas have the same prognosis as sporadic soft tissue sarcomas? J Clin Oncol. 2010;28(12):2064–9.
3. Canadian Cancer Society. http://www.cancer.ca/en/cancer-information/cancer-type/soft-tissue-sarcoma/statistics/?region=on
4. Brennan MF, Antonescu CR, Maki RG. General description. In: Brennan MF, editor. Management of soft tissue sarcoma. New York: Springer; 2013. p. 6.
5. Heslin MJ, Lewis JJ, Nadler E, et al. Prognostic factors with long-term survival for retroperitoneal sarcoma: implications for management. J Clin Oncol. 1997;15(8):2832–9.
6. Linehan DC, Lewis JJ, Leung D, et al. Influence of biologic factors and anatomic site in completely resected liposarcoma. J Clin Oncol. 2000;18(8):1637–43.
7. Lewis JJ, Leung D, Woodruff JM, et al. Retroperitoneal sarcoma: analysis of 500 patients treated and followed at a single institution. Ann Surg. 1998;228(3):355–65.
8. Catton CN, O'Sullivan B, Kotwall C, et al. Outcome and prognosis in retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys. 1994;29(5):1005–10.
9. Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F. World Health Organization classification of tumours of soft tissue and bone. 4th ed. Lyon: IARC Press; 2013.
10. Sherman KL, Kinnier CV, Farina DA, et al. Examination of national lymph node evaluation practices for adult extremity soft tissue sarcoma. J Surg Oncol. 2014;110(6):682–8.
11. Riad G, Griffim AM, Liberman B, et al. Lymph node metastasis in soft tissue sarcoma in an extremity. Clin Orthop Relat Res. 2004;426:129–34.
12. Johannesmeyer D, Smith V, Cole DJ, et al. The impact of lymph node disease in extremity soft-tissue sarcomas: a population-based analysis. Am J Surg. 2013;206(3):289–95.
13. Fong Y, Coit DG, Woodruff JM, et al. Lymph node metastasis from soft tissue sarcoma in adults. Analysis of data from a prospective database of 1772 sarcoma patients. Ann Surg. 1993;217(1):72–7.
14. Pisters PW, Leung DH, Woodruff J, et al. Analysis of prognostic factors in 1,041 patients with localized soft tissue sarcomas of the extremities. J Clin Oncol. 1996;14(5):1679–89.
15. Singer S, Antonescu CR, Riedel E, Brennan MF. Histologic subtype and margin of resection predict pattern of recurrence and survival for retroperitoneal liposarcoma. Ann Surg. 2003;238:358–70.
16. Gronchi A, Casali PG, Fiore M, et al. Retroperitoneal soft tissue sarcomas: patterns of recurrence in 167 patients treated at a single institution. Cancer. 2004;100(11):2448–55.
17. Alldinger I, Yang Q, Pilarsky C, et al. Retroperitoneal soft tissue sarcomas: prognosis and treatment of primary and recurrent disease in 117 patients. Anticancer Res. 2006;26(2B):1577.
18. Christie-Large M, James SL, Tiessen L, et al. Imaging strategy for detecting lung metastases at presentation in patients with soft tissue sarcomas. Eur J Cancer. 2008;44(13):1841–5.
19. Edge SB, Byrd DR, Compton CC, et al., editors. AJCC (American Joint Committee on Cancer). Cancer staging manual. 7th ed. New York: Springer; 2010.

20. Van Dalen T, Van Coevorden F, et al. Evaluation of a clinically applicable postsurgical staging system for primary retroperitoneal soft tissue sarcoma. Ann Surg. 2004;11:483.
21. Kattan MW, Leung DHY, Brennan MF. Postoperative nomogram for 12-year sarcoma-specific death. J Clin Oncol. 2002;20:791–6.
22. Dalal KM, Kattan MW, Antonescu CR, et al. Subtype specific prognostic nomogram for patients with primary liposarcoma of the retroperitoneum, extremity or trunk. Ann Surg. 2006;244(3):381–91.
23. National Comprehensive Cancer Network. Clinical Practice Guidelines: Soft Tissue Sarcoma (2.2014). http://www.nccn.org/professionals/physician_gls/pdf/sarcoma.pdf. Accessed 9 Nov 2014.
24. Stoeckle E, Coindre JM, Bonvalot S, et al. Prognostic factors in retroperitoneal sarcoma: a multivariate analysis of a series of 165 patients of the French Cancer Center Federation Sarcoma Group. Cancer. 2001;92:359–68.
25. Jones JJ, Catton CN, O'Sullivan B, et al. Initial results of a trial of preoperative external-beam radiation therapy and postoperative brachytherapy for retroperitoneal sarcoma. Ann Surg Oncol. 2002;9(4):346.
26. Pawlik TM, Pisters PW, Mikula L, et al. Long-term results of two prospective trials of preoperative external beam radiotherapy for localized intermediate or high-grade retroperitoneal soft tissue sarcoma. Ann Surg Oncol. 2006;13:508–17.
27. http://www.clinicaltrials.gov/ct2/show/NCT01344018?term=EORTC+and+preoperative+radiation+therapy&rank=2. Accessed 7 Nov 2014.
28. Tseng WH, Martinez SR, Tamurian RM, et al. Contiguous resection is safe in patients with retroperitoneal sarcoma: an ACS-NSQIP analysis. J Surg Oncol. 2011;103(5):390–4.
29. Bonvalot S, Miceli R, Berselli M, et al. Aggressive surgery in retroperitoneal soft tissue sarcoma carried out at high-volume centers is safe and is associated with improved local control. Ann Surg Oncol. 2010;17(6):1507–14.
30. Mendenhall WM, Zlotecki RA, Hochwald SN, et al. Retroperitoneal soft tissue sarcoma. Cancer. 2005;104(4):669.
31. Park JO, Qin LX, Prete FP, et al. Predicting outcome by growth rate of locally recurrent retroperitoneal liposarcoma: the one centimeter per month rule. Ann Surg. 2009;250(6):977–82.
32. Issels RD, Lindner LH, Verweij J, et al. European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group (EORTC-STBSG), European Society for Hyperthermic Oncology (ESHO). Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. Lancet Oncol. 2010;11(6):561.
33. Billingsley KG, Burt ME, Jara E, et al. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg. 1999;229(5):602.
34. van Geel AN, Pastorino U, Jauch KW, et al. Surgical treatment of lung metastases: The European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group study of 255 patients. Cancer. 1996;77(4):675.
35. Choong PF, Pritchard DJ, Rock MG, et al. Survival after pulmonary metastasectomy in soft tissue sarcoma. Prognostic factors in 214 patients. Acta Orthop Scand. 1995;66(6):561.
36. Pawlik TM, Vauthey JN, Abdalla EK, et al. Results of a single-center experience with resection and ablation for sarcoma metastatic to the liver. Arch Surg. 2006;141(6):537.
37. Chua TC, Chu F, Morris DL. Outcomes of single-centre experience of hepatic resection and cryoablation of sarcoma liver metastases. Am J Clin Oncol. 2011;34(3):317.
38. Lang H, Nussbaum KT, Kaudel P, et al. Hepatic metastases from leiomyosarcoma: a single-center experience with 34 liver resections during a 15-year period. Ann Surg. 2000;231(4):500–5.
39. O'Sullivan B, Davis AM, Turcotte R, et al. Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. Lancet. 2002;359(9325):2235.
40. Al-Refaie WB, Habermann EB, Jensen EH, et al. Surgery alone is adequate treatment for early stage soft tissue sarcoma of the extremity. Br J Surg. 2010;97(5):707.

41. Williard WC, Hajdu SI, Casper ES, Brennan MF. Comparison of amputation with limb-sparing operations for adult soft tissue sarcoma of the extremity. Ann Surg. 1992;215(3):269.
42. Rosenberg SA, Tepper J, Glatstein E, et al. The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of limb-sparing surgery plus radiation therapy compared with amputation and the role of adjuvant chemotherapy. Ann Surg. 1982;196(3):305–15.
43. Wilson AN, Davis A, Bell RS, et al. Local control of soft tissue sarcoma of the extremity: the experience of a multidisciplinary sarcoma group with definitive surgery and radiotherapy. Eur J Cancer. 1994;30A(6):746.
44. McGee L, Indelicato DJ, Dagan R, et al. Long-term results following postoperative radiotherapy for soft tissue sarcomas of the extremity. Int J Radiat Oncol Biol Phys. 2012;84(4):1003–9.
45. Lans TE, Grünhagen DJ, de Wilt JH, et al. Isolated limb perfusions with tumor necrosis factor and melphalan for locally recurrent soft tissue sarcoma in previously irradiated limbs. Ann Surg Oncol. 2005;12(5):406–11.
46. Sindelar WF, Kinsella TJ, Chen PW, et al. Intraoperative radiotherapy in retroperitoneal sarcomas. Final results of a prospective, randomized, clinical trial. Arch Surg. 1993;128:402–10.
47. Gieschen HL, Spiro IJ, Suit HD, et al. Long-term results of intraoperative electron beam radiotherapy for primary and recurrent retroperitoneal soft tissue sarcoma. Int J Radiat Oncol Biol Phys. 2001;50:127–31.
48. Smith MJ, Ridgway PF, Catton CF, et al. Combined management of retroperitoneal sarcoma with dose intensification radiotherapy and resection: long-term results of a prospective trial. Radiother Oncol. 2014;110(1):165–71.
49. Pisters PW, Harrison LB, Leung DH, et al. Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. J Clin Oncol. 1996;14:859–68.
50. Yang JC, Chang AE, Baker AR, et al. Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. J Clin Oncol. 1998;16:197–203.
51. Bramwell VH, Anderson D, Charette ML, Sarcoma Disease Site Group. Doxorubicin-based chemotherapy for the palliative treatment of adult patients with locally advanced or metastatic soft tissue sarcoma. Cochrane Database Syst Rev. 2003;3:CD003293. Review.
52. Jones RL, Fisher C, Al-Muderis O, et al. Differential sensitivity of liposarcoma subtypes to chemotherapy. Eur J Cancer. 2005;41(18):2853–60.
53. Rosen G, Forscher C, Lowenbraun S, et al. Synovial sarcoma. Uniform response of metastases to high dose ifosfamide. Cancer. 1994;73(10):2506–11.
54. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Sarcoma Meta-analysis Collaboration. Lancet. 1997;350:1647–54.
55. Pervaiz N, Colterjohn N, Farrokhyar F, et al. A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma. Cancer. 2008;113:573–81.
56. Frustaci S, Gherlinzoni F, De Paoli A, et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: results of the Italian randomized cooperative trial. J Clin Oncol. 2001;19:1238–47.
57. Nesbit Jr ME, Gehan EA, Burgert Jr EO, et al. Multimodal therapy for the management of primary, nonmetastatic Ewing's sarcoma of bone: a long-term follow-up of the First Intergroup study. J Clin Oncol. 1990;8:1664–74.
58. Arndt CA, Stoner JA, Hawkins DS, et al. Vincristine, actinomycin, and cyclophosphamide compared with vincristine, actinomycin, and cyclophosphamide alternating with vincristine, topotecan, and cyclophosphamide for intermediate-risk rhabdomyosarcoma: children's oncology group study D9803. J Clin Oncol. 2009;27(31):5182–8.
59. Ferrario T, Karakousis CP. Retroperitoneal sarcomas: grade and survival. Arch Surg. 2003;138(3):248–51.
60. Catton C, Davis A, Bell R, et al. Soft tissue sarcoma of the extremity. Limb salvage after failure of combined conservative therapy. Radiother Oncol. 1996;41:209–14.

Chapter 23
Thyroid Cancer

Vanessa Palter, Karen Devon, Lorne E. Rotstein, and Robert Tasevski

Introduction

Epidemiology

Since 1998, thyroid cancer has had the greatest increase in incidence of all cancers in Canada (6.2 % per year in males and 4.3 % per year in females) [1]. Mortality rates however have remained stable. The Canadian Cancer Society (CCS) has estimated 6000 new cases for 2014 (77 % females), with an incidence rate of 14.5 per 100,000 [1].

V. Palter, M.D., Ph.D., F.R.C.S.C. (✉)
Fellow, General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: vanessa.palter@mail.utoronto.ca

K. Devon, M.D., M.Sc., F.R.C.S.C., F.A.C.S. • L.E. Rotstein, M.D., F.A.C.S., F.R.C.S.C.
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: karen.devon@wchospital.ca ; lorne.rotstein@uhn.ca

R. Tasevski, M.B.B.S., M.Sc., F.R.A.C.S.
Department of Surgery, University of Melbourne, Melbourne, Australia
e-mail: robert.tasevski@mh.org.au

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5_23

Prognosis according to subtype of thyroid carcinoma

Thyroid Carcinoma (TC) Subtype	Prognosis 10-year overall survival (OS)
• Differentiated Thyroid Carcinoma—DTC (90 %) – Papillary thyroid carcinoma (80 %) – Tall cell variant (5–10 % of papillary) – Hobnail variant (rare) – Follicular thyroid carcinoma (5–10 %) – Hurthle cell carcinoma (<5 %)	95–98 % 70–80 % 30–50 % 85–90 % 70–75 %
• Undifferentiated Thyroid Carcinoma (1 %) – Anaplastic (1 %)	3–5 %
• Medullary Thyroid Carcinoma—MTC (5 %) – Sporadic (4 % of TC or 80 % of MTC) – Inherited (1 % TC or 20 % MTC)	75–80 %

The remaining 5 % of thyroid cancers comprises rare types such as lymphoma and metastases to the thyroid gland.

Staging and Prognostic Scoring Schemes

In the past three decades, several systems have been proposed to stage differentiated thyroid cancer: AGES [2], AMES [3], MSKCC [4], MACIS [5], Ohio State [6], EORTC (European Organization for Research on Treatment of Cancer) [7], NTCTCS (National Thyroid Cancer Treatment Cooperative Study) [8], and AJCC (American Joint Committee on Cancer) [9].

Currently, we recommend the AJCC 7th edition as the staging system for thyroid carcinomas. The MACIS system is preferentially utilized for prognosis and deciding which patients are appropriate for radioactive iodine therapy.

Definitions/Terminology

- **Lobectomy:** the complete removal of one lobe of the thyroid, including the isthmus.
- **Hemithyroidectomy:** same as lobectomy.
- **Total thyroidectomy:** the complete removal of both thyroid lobes, isthmus and pyramidal lobe of the thyroid gland.
- **Near-total thyroidectomy:** the near complete removal of all thyroid tissue, leaving only a small amount (<1 g) of tissue adjacent to the recurrent laryngeal nerve near the ligament of Berry. This should be clearly defined in the operation notes.
- The terms **sub-total lobectomy** and **sub-total thyroidectomy** are imprecise and should be avoided.
- **Central Neck Compartment:** the central neck is bounded superiorly by the hyoid bone, laterally by the carotid arteries, and inferiorly by the brachiocephalic

(innominate) artery on the right and the corresponding axial plane on the left (i.e., levels VI and VII). This space contains prelaryngeal (Delphian), pretracheal, and the right and left paratracheal lymph node basins.

- **Central Neck Dissection:** involves comprehensive, compartment-oriented removal of the prelaryngeal and pretracheal and at least one paratracheal lymph node basin. A designation should be made as to whether unilateral or bilateral dissection is performed, and on which side (left or right) in unilateral cases. A therapeutic central neck dissection implies that nodal metastases are apparent clinically (preoperatively or intraoperatively) or by imaging. A prophylactic or elective central neck dissection implies that nodal metastases are not detected clinically or by imaging. Currently the role of prophylactic central neck dissection remains controversial.
- **Microcarcinoma:** papillary thyroid cancer with diameter ≤ 1 cm.

Risk of Recurrence

The 2015 American Thyroid Association (ATA) guidelines classify surgically treated differentiated thyroid carcinoma into a three tiered system to predict the risk of recurrent or metastatic disease [10].

ATA low risk	ATA intermediate risk	ATA high risk
• Papillary thyroid cancer with ALL of the following: – No local or distant metastases – Macroscopic tumor completely resected – No locoregional invasion – No aggressive histology – no vascular invasion – If RAI given no uptake outside thyroid bed – Clinical N0 or ≤5 pathologic micrometastases (≤0.2 cm) • Intrathyroidal microcarcinoma (uni- or multi-focal) • Intrathyroidal well differentiated follicular carcinoma: – with only capsular invasion – with only minor vascular invasion	• Papillary thyroid cancer with ANY of the following: – Microscopic invasion into perithyroidal soft tissues – RAI avid metastatic foci in the neck – Aggressive histology (tall cell, hobnail, columnar) – Vascular invasion – Clinical N1 – >5 pathological N1 with all involved nodes <3 cm • Intrathyroidal papillary cancer 1–4 cm (BRAF mutated if known) • Multifocal papillary microcarcinoma with extrathyroidal extension (BRAF mutated if known)	• Papillary thyroid cancer with ANY of the following: – Macroscopic tumor invasion into perithyroidal soft tissue – Incomplete tumor resection – Distant metastases – pathologic N1 with largest node >3 cm – Postoperative TG suggestive of metastatic disease • Follicular carcinoma with: – extensive vascular invasion (>4 foci)

Thyroid Nodules

Initial Assessment [10]

The management of a patient with a thyroid nodule that is incidentally discovered includes:

- History
  - Childhood head and neck irradiation
  - Irradiation for bone-marrow transplantation
  - Exposure to ionizing radiation
  - Familial cancer syndromes
- Physical examination for factors suggesting malignancy
  - Vocal cord paralysis
  - Cervical lymphadenopathy
  - Fixation of the nodule
- TSH
  - If TSH subnormal then perform radionucleotide scan
  - If scan is "hot," then further investigation regarding the patient's clinical/subclinical hypothyroidism is required
- Ultrasound of the thyroid and neck (if not already performed)

When to Perform FNA [10]

FNA of a thyroid nodule is recommended for:

1. Nodules ≥1 cm with high OR intermediate suspicion sonographic pattern (see below).
2. Nodules ≥1.5 cm with low suspicion sonographic pattern.
3. Nodules ≥2 cm with very low suspicion sonographic pattern.

Conversely, FNA is NOT recommended for nodules that do not meet the above criteria or nodules that are purely cystic.

Ultrasound Features of Malignancy [10]

1. High suspicion sonographic pattern (malignancy risk >70–90 %)
   (a) Solid hypoechoic nodule with one or more of the following features:
      - Irregular margins
      - Microcalcifcations
      - Taller rather than wide
      - Disrupted rim calcification with hypoechoic extrusive soft tissue component
      - Extrathyroidal extension
2. Intermediate suspicion sonographic pattern (malignancy risk 10–20 %)
   (b) Solid hypoechoic nodule with:
      - Smooth regular margin
      - No microcalcifications
      - No extrathyroidal extension
      - Not taller than wide
3. Low suspicion malignancy (malignancy risk 5–10 %)
   (c) Isoechoic or hyperechoic nodule with none of the high suspicion features
4. Very low suspicion malignancy (malignancy risk <3 %)
   (d) Spongiform or partially cystic nodules without any of the high suspicion features
5. Benign (malignancy risk <1 %)
   (e) Purely cystic nodules

Management of FNA Cytology

In order to ensure consistency in FNA cytology reporting, in 2007, the Bethesda criteria were developed. The Bethesda criteria describes six diagnostic categories for FNA and provides an estimate of cancer risk for each [10–12].

Diagnostic category	Risk of malignancy (%) [12]	Management [10]
Non diagnostic/unsatisfactory	1–4	• Repeat FNA with U/S guidance (do >3 months after 1st FNA) • If second FNA is non-diagnostic observation or surgery are options depending on U/S characteristics
Benign	0–3	• No further treatment required
Atypia of undetermined significance OR Follicular lesion of undetermined significance (AUS/FLUS)	5–15	• Repeat FNA +/− molecular testing • If repeat FNA still inconclusive observation or surgery are options depending on U/S characteristics
Follicular neoplasm OR Suspicious for a follicular neoplasm	15–30	• Molecular testing to better assess malignancy risk[a] • If molecular testing not performed or inconclusive: surgery for diagnosis
Suspicious for malignancy	60–75	• Surgery
Malignant	97–99	• Surgery

[a]A number of molecular markers have been proposed for indeterminate cytology determination. These include BRAF and RAS mutational status amongst others [13]. While this is becoming standard of practice in the US, as of yet, these assays are not available in Canada

Differentiated Thyroid Cancer (DTC)

DTC: Primary Localized Disease

Workup	Surgical Treatment		Adjuvant Treatment			Follow-up (F/U) [10]	
	Primary [10]	Lymph Node Assessment [10]	Radioactive Iodine (RAI) (I ablation^{131}) [10]	External Beam Radiotherapy (EBRT) [14, 15]	TSH	Low Risk	High Risk
• History and physical exam • Labs: – TSH, FT3, FT4 • Direct or indirect laryngoscopy (vocal cord assessment) • Imaging: – Neck US – Neck CT scan with contrast • FNA of clinically or radiologically suspicious LN (cytology ±measurement of Tg in needle washout)	• Total Thyroidectomy (any of the following): – Tumor ≥ 4 cm – Extrathyroidal extension – Regional or distant metastases • Total Thyroidectomy OR Hemithyroidectomy – Tumor 1–4 cm – No extrathyroidal extension – No lymph node metastases • Hemithyroidectomy (if all present): – Tumor < 1 cm – No extrathyroidal extension – Unifocal – No cervical lymph nodes – No familial thyroid carcinoma – No previous head or neck irradiation	• Therapeutic Central Compartment dissection: – Clinically involved nodes • Therapeutic Lateral Compartment dissection – Clinically involved lateral compartment nodes • Prophylactic central compartment dissection – controversial – consider if: – T3 or 4 tumors – clinically involved lateral nodes	• Routinely recommended: – ATA High risk patients—30 to 150 mCi • Considered: – ATA Intermediate risk patients • Not Routinely recommended: – ATA low risk patients – Multifocal or unifocal micropapillary carcinoma in the absence of other high risk features	• Controversial • Potential benefit from EBRT: – Highly selected patients >60 with extrathyroidal extension and no gross residual disease – Patients with serial operations to palliate local disease	• ATA high risk patients – TSH < 0.1 mU/L • ATA intermediate risk patients – TSH 0.1–0.5 mU/L • ATA Low risk patients who are clinically free of disease: – Thyroxine replacement without complete suppression of TSH – TSH 0.5–2 mU/L	• Annually: – Physical exam – Neck US (at 6–12 months then frequency depends on patient factors) – TSH levels – Serum Tg and anti-Tg levels (q12–24 months) (see special notes below)	• Annually: – Physical exam – Neck US – TSH levels – Serum Tg and anti-Tg levels (6-12 q mo) (see special notes below)

EBRT external beam radiotherapy, *RAI* radioactive iodine, *LN* lymph node, *TSH* thyroid stimulating hormone, *Serum Tg* thyroglobulin, *FNA* fine needle aspiration, *DTC* differentiated thyroid carcinoma

Special Notes

- Recommendations for completion thyroidectomy are similar to indications of total thyroidectomy.
- Low-risk patients follow-up:
  - If RAI ablation performed, TSH stimulated Tg at 6–12 months post RAI. If TSH stimulated Tg is undetectable, then can be followed with TSH-suppressed Tg
- High-risk patients follow-up:
  - Diagnostic TSH stimulated RAI whole body scan 6–12 months after remnant ablation (with thyroid hormone withdrawal or rhTSH if available) [14]
- Consider intraoperative frozen section for suspicious lymph node if deciding whether or not to do a compartmental dissection
- Consensus guidelines from the ATA provide decision-making aides regarding which patients are suitable for outpatient thyroidectomy [16].
- Currently in Toronto, well patients who undergo uncomplicated hemithyroidectomies are discharged home after a 6 h observation period

DTC: Regional Metastatic Disease

Clinical scenario	Surgical approach
Suspicious LN in Central Neck (during surgery)	• Central Neck (Level VI) Dissection
Suspicious LN in Lateral Neck (during surgery)	• Confirm presence of metastatic node radiologically and with cytology • Staged functional Compartmental Neck Dissection (Level 2A to 5B) and Central Neck (Level VI) Dissection
Positive LN in Central Neck (imaging/palpation)	• Central Neck (Level VI) Dissection
Positive LN in Lateral Neck (imaging/palpation with cytological confirmation)	• Functional Compartmental Neck Dissection (Level 2A to 5B) and Central Neck (Level VI) Dissection

DTC: Distant Metastatic Disease

Workup	Surgical approach	Therapeutic options[a]
• Labs: – Serum thyroglobulin • Imaging: – CT scan brain, chest, abdomen, pelvis – Bone scan – Diagnostic whole-body RAI scan – Consider PET scan with thyrogen stimulation to better define extent of tumor, especially in those that do not concentrate RAI [17]	• Metastectomy: – Careful consideration in selected patients with solitary lesions (preferred approach for CNS lesions) – Surgical palliation	• Lung: – RAI 200 mCi-I^{131} – Conventional systemic therapy, e.g., doxorubicin (if non-RAI-avid) – Consider TKI (if non-RAI-avid) • Bone: – RAI 200 mCi-I^{131} – If not resectable and symptomatic or fracture or neurologic compromise possible, consider EBRT 50Gy in 25 fraction

EBRT external beam radiotherapy, *RAI* radioactive iodine, *PET* positron emission tomography, *CNS* central nervous system

[a]Consider offering participation in clinical trials

Medullary Thyroid Cancer (MTC)

Sporadic MTC

Workup [18]	Surgical treatment		External beam radiotherapy (EBRT) [18]	Follow-up (F/U)
	Primary [18]	Lymph node assessment [18]		
• Same as DTC plus: – Serum CEA levels – Serum calcitonin – 24-h urine or plasma catecholamines and metanephrines – Serum calcium and intact PTH levels – CT scan neck/chest/abdo – Mutational analysis of RET oncogene – Genetic counseling	• Total thyroidectomy plus bilateral central compartment dissection	• Ipsilateral functional compartmental neck dissection (2A-5B) – Patients with clinically involved lateral compartment nodes – Considered for prophylaxis in patients with LN metastases in the central neck compartment (controversial)	• Adjuvant if: – Consider for R1 resection for moderate to high volume disease – Consider for R0 resection for moderate to high volume disease with extra-nodal soft tissue extension and detectable post-op calcitonin in absence of distant metastases • Therapeutic if: – R2 resection	• If basal calcitonin not detectable, annual: – Physical exam – Calcitonin and CEA levels – Neck US • If basal calcitonin detectable (see special notes below)

DTC differentiated thyroid cancer, *EBRT* external beam radiotherapy, *CEA* carcinoembryonic antigen

Special Notes

- Follow-up with detectable basal calcitonin:
  - Calcitonin and CEA every 6 months to determine doubling time. Ongoing F/U should occur at 1/4th the shortest doubling time. Anatomic imaging based on stability of calcitonin, symptoms, location of known/likely metastases.
- In the presence of metastatic disease:
  - thyroidectomy, plus central compartment dissection to prevent local symptoms.

Familial MTC (MEN 2A, MEN 2B and Familial Non-MEN MTC [FMTC])

	Workup	Surgical treatment		External beam radiotherapy (EBRT)	Follow-up (F/U)
		Primary	Lymph node assessment		
MEN 2A (most common 70 %)	• Same as sporadic MTC • Average age: 5–25 years old	• As per sporadic MTC for clinically apparent disease • Prophylactic surgery: – Total thyroidectomy • Primary HPT: – Total parathyroidectomy with autotransplantation or subtotal parathyroidectomy	• Clinically apparent MTC: – As per sporadic MTC • Prophylactic surgery: – Prophylactic CND (level VI) only if clinical/radiological evidence LN mets, nodules >5 mm and calcitonin>40 pg/mL	• As per sporadic MTC	• Same as sporadic MTC plus: – Annual 24-h urine or plasma catecholamines or metanephrines – Adrenal imaging with MRI or CT if urine/plasma catecholamines or metanephrines elevated – Annual serum calcium and intact PTH levels
FMTC (20 %)	• Same as sporadic MTC	• As per MEN 2A	• As per MEN 2A	• As per sporadic MTC	• Same as sporadic MTC

MEN 2B (10 %)	• Same as sporadic MTC • Average age: first year of life	• As per sporadic MTC for clinically apparent disease • Prophylactic surgery: – Total thyroidectomy	• Clinically apparent MTC: – As per sporadic MTC • Prophylactic surgery (≤1 y.o.): – Prophylactic CND only if clinical or radiological evidence LN mets, nodules > 5 mm and calcitonin > 40 pg/mL • Prophylactic surgery (>1 y.o.): – Prophylactic CND	• As per sporadic MTC	• Same as sporadic MTC plus: – Annual 24-h urine or plasma catecholamines or metanephrines – Adrenal imaging with MRI or CT if urine/plasma catecholamines or metanephrines elevated

- Prophylactic Surgery offered to gene carriers [19]:
- For the timing of surgery for MEN carriers refer to the ATA guidelines as the timing of the surgery depends on the type of mutation [18]
  - MEN 2B (high risk ATA level D RET mutations): total thyroidectomy within the first year of life
  - MEN 2A:
    Low risk ATA level A and B RET mutations: thyroidectomy around 5 years of age
    High risk ATA level C RET mutations: thyroidectomy before 5 years of age

The complete management of MEN 2 syndromes is beyond the scope of this chapter
HPT hyperparathyroidism, *EBRT* external beam radiotherapy, *CND* central neck dissection, *MEN* multiple endocrine neoplasia syndrome

Special Notes

- The high risk of anesthesia and surgery in the presence of a pheochromocytoma dictates that its management takes the highest surgical priority.
- Surgical management of primary hyperparathyroidism at the time of initial thyroidectomy should always be performed if the diagnosis of hyperparathyroidism is established.
- FMTC:
  - At least four affected relatives with MTC alone (mild and clinical variant of MEN 2A)

Pregnancy and Thyroid Cancer

	Workup	Surgical treatment	Adjuvant treatment	Follow-up (F/U)
Diagnosed during First Trimester	• Serum calcitonin levels • Ob/Gyn: – Ultrasound each trimester tracking development of fetus • TSH and FT4 every month	• Do not interrupt pregnancy • Surgery after delivery • Discuss and consider surgery during 2nd trimester if: – Medullary thyroid cancer – Tumor growth (>50 %) – Evidence of lymph node metastases	• If Radioactive Iodine therapy is indicated, this should be provided when the patient is not breast-feeding	• Similar to previously described (DTC, MTC or Anaplastic)
Diagnosed during Second Trimester	• Same as above	• Same as above	• Same as above	• Same as above
Diagnosed during Third Trimester	• Same as above	• Do not interrupt pregnancy • Surgery after delivery	• Same as above	• Same as above

TSH thyroid-stimulating hormone, *FT4* Free T4 = Free Thyroxine, *DTC* differentiated thyroid cancer, *MTC* medullary thyroid carcinoma

Special Notes

- There is no evidence that DTC during pregnancy portends a worse prognosis. There is no difference in local recurrence, distant recurrence or overall survival when comparing pregnant and nonpregnant women.
- When surgery is performed during the first trimester, spontaneous abortion rates are higher [20].
- Thyroid surgery during pregnancy is associated with higher rates of surgical complications, longer length of hospital stay and higher hospital costs.

Anaplastic Thyroid Carcinoma

Workup	Surgical treatment	External beam radiotherapy	Chemotherapy	Follow-up (F/U)
• Imaging: – CT scan of neck and thorax • Core biopsy to differentiate from lymphoma	• Very limited role • Consider: – Biopsy for diagnosis – Airway management	• Radical Radiotherapy: – Unresectable local disease, with no evidence of distant spread and good performance status – Radiotherapy (40 Gy/20 fractions) following chemotherapy for small cell anaplastic	• To consider in small cell anaplastic cancers	• Tumor response by physical exam

Surgical Technologies

- Intraoperative neuromonitoring [21, 22]
  - Aids in the identification of the recurrent laryngeal nerve
  - Does not prevent nerve injury to the recurrent laryngeal nerve
  - Decreases injury to the external branch of the superior laryngeal nerve
  - Most useful in reoperative procedures
- Hemostatic devises
  - LigaSure device and Harmonic scalpel
  - There is no convincing evidence that either is superior with respect to operative time, intraoperative blood loss, parathyroid preservation or reduction in nerve injury [23–26].
  - When compared to conventional hemostatic techniques, both provide a reduction in operative time [23, 24] .

Relevant Publications

Study	Methods	Results
American Thyroid Association (ATA) Guidelines [10]	• Consensus and evidence-based guidelines	• Management guidelines for thyroid differentiated thyroid cancer
American Thyroid Association (ATA) Guidelines [18]	• Consensus and evidence-based guidelines	• Management guidelines for medullary thyroid cancer
Billimoria KY et al. [27]	• Retrospective review • 52,173 patients from the National Cancer Data Base • Patients with tumors > 1 cm: thyroid lobectomy vs. total thyroidectomy	• Total thyroidectomy group: – Increased survival ($P = 0.009$) – Decreased recurrence rates ($P = 0.04$)
SEER Database Study Podnos et al. [28]	• Retrospective • $N = 20{,}000$	• Survival in DTC is adversely affected by lymph node metastases • 14-y OS 82 % node negatives vs. 79 % node positives; $p < 0.05$

Referring to Multidisciplinary Cancer Conference (MCC)

1. All medullary thyroid carcinomas
2. Complex DTC cases
3. Locally advanced DTC
4. All anaplastic thyroid carcinomas

Toronto Pearls

- Bilateral superficial cervical plexus blockade for all thyroidectomies using bupivacaine with epinephrine.
- The recurrent laryngeal nerve should be identified and preserved in virtually all instances.
- When the recurrent laryngeal nerve is identified, this is just the onset of the operation, which encompasses a thorough nerve dissection.
- Attempts should be made to preserve the external branch of the superior laryngeal nerve, by ligation of the superior thyroid vessels at the capsule of the thyroid gland, as well as attempted visualization.

- Parathyroid glands should, whenever possible, be identified and preserved. If the vascular supply is deemed to be compromised, the gland should be excised, biopsied, and re-implanted into muscle (i.e., sternocleidomastoid).
- We discourage the routine practice of intraoperative frozen section analysis on thyroid specimens.
- Decisions regarding extent of surgery should be made preoperatively.

References

1. Canadian Cancer Society's Advisory Committee on Cancer. Canadian Cancer Statistics 2014. Accessed December 2014. Cancer.ca
2. Hay ID, Grant CS, Taylor WF, McConahey WM. Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery. 1987;102(6):1088–95.
3. Cady B, Rossi R. An expanded view of risk-group definition in differentiated thyroid carcinoma. Surgery. 1988;104(6):947–53.
4. Shah JP, Loree TR, Dharker D, et al. Prognostic factors in differentiated carcinoma of the thyroid gland. Am J Surg. 1992;164(6):658–61.
5. Hay ID, Bergstralh EJ, Goellner JR, et al. Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery. 1993;114(6):1050–7. discussion 1057–8.
6. Mazzaferri EL, Jhiang SM. Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med. 1994;97(5):418–28.
7. Byar DP, Green SB, Dor P, et al. A prognostic index for thyroid carcinoma. A study of the E.O.R.T.C. Thyroid Cancer Cooperative Group. Eur J Cancer. 1979;15(8):1033–41.
8. Sherman SI, Brierley JD, Sperling M, et al. Prospective multicenter study of thyroid carcinoma treatment: initial analysis of staging and outcome. National Thyroid Cancer Treatment Cooperative Study Registry Group. Cancer. 1998;83(5):1012–21.
9. Edge S, Byrd DR, Compton CC, et al. AJCC cancer staging manual. 7th ed. New York: Springer; 2010. p. 87–96.
10. Haugen BR, Alexander EK, Bible KC, et al. American thyroid association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid. 2015 Oct 14. [Epub ahead of print].
11. Baloch ZW, LiVolsi VA, Asa SL, et al. Diagnostic terminology and morphologic criteria for cytologic diagnosis of thyroid lesions: a synopsis of the National Cancer Institute Thyroid Fine-Needle Aspiration State of the Science Conference. Diagn Cytopathol. 2008;36(6):425–37.
12. Crippa S, Mazzucchelli L, Cibas ES, Ali SZ. The Bethesda System for reporting thyroid fine-needle aspiration specimens. Am J Clin Pathol. 2010;134(2):343–4. author reply 345.
13. Xing M, Haugen BR, Schlumberger M. Progress in molecular-based management of differentiated thyroid cancer. Lancet. 2013;381(9871):1058–69.
14. Wilson PC, Millar BM, Brierley JD. The management of advanced thyroid cancer. Clin Oncol (R Coll Radiol). 2004;16(8):561–8.
15. Terezakis SA, Lee KS, Ghossein RA, et al. Role of external beam radiotherapy in patients with advanced or recurrent nonanaplastic thyroid cancer: Memorial Sloan-kettering Cancer Center experience. Int J Radiat Oncol Biol Phys. 2009;73(3):795–801.
16. Terris DJ, Snyder S, Carneiro-Pla D, et al. American Thyroid Association statement on outpatient thyroidectomy. Thyroid. 2013;23(10):1193–202.

17. Larson SM, Robbins R. Positron emission tomography in thyroid cancer management. Semin Roentgenol. 2002;37(2):169–74.
18. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid. 2009;19(6):565–612.
19. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab. 2001;86(12):5658–71.
20. Moosa M, Mazzaferri EL. Outcome of differentiated thyroid cancer diagnosed in pregnant women. J Clin Endocrinol Metab. 1997;82(9):2862–6.
21. Snyder SK, Hendricks JC. Intraoperative neurophysiology testing of the recurrent laryngeal nerve: plaudits and pitfalls. Surgery. 2005;138(6):1183–91. discussion 1191–2.
22. Calo PG, Pisano G, Medas F, et al. Identification alone versus intraoperative neuromonitoring of the recurrent laryngeal nerve during thyroid surgery: experience of 2034 consecutive patients. J Otolaryngol Head Neck Surg. 2014;43:16.
23. Pons Y, Gauthier J, Ukkola-Pons E, et al. Comparison of LigaSure vessel sealing system, harmonic scalpel, and conventional hemostasis in total thyroidectomy. Otolaryngol Head Neck Surg. 2009;141(4):496–501.
24. Macario A, Dexter F, Sypal J, et al. Operative time and other outcomes of the electrothermal bipolar vessel sealing system (LigaSure) versus other methods for surgical hemostasis: a meta-analysis. Surg Innov. 2008;15(4):284–91.
25. Rahbari R, Mathur A, Kitano M, et al. Prospective randomized trial of ligasure versus harmonic hemostasis technique in thyroidectomy. Ann Surg Oncol. 2011;18(4):1023–7.
26. Lang BH, Ng SH, Lau LL, et al. A systematic review and meta-analysis comparing the efficacy and surgical outcomes of total thyroidectomy between harmonic scalpel versus ligasure. Ann Surg Oncol. 2013;20(6):1918–26.
27. Bilimoria KY, Bentrem DJ, Ko CY, et al. Extent of surgery affects survival for papillary thyroid cancer. Ann Surg. 2007;246(3):375–81. discussion 381–4.
28. Podnos YD, Smith D, Wagman LD, Ellenhorn JD. The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg. 2005;71(9):731–4.

Index

F.C. Wright et al. (eds.), *Surgical Oncology Manual*,
DOI 10.1007/978-3-319-26276-5